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(54) Title: HIGH AFFINITY TGF β NUCLEIC ACID LIGANDS AND INHIBITORS		
(57) Abstract Methods are described for the identification and preparation of high-affinity nucleic acid ligands to TGF β . Included in the invention are specific RNA ligands to TGF β 1 identified by the SELEX method. Also included are RNA ligands that inhibit the interaction of TGF β 1 with its receptor.		

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HIGH AFFINITY TGF β NUCLEIC ACID LIGANDS AND INHIBITORS

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FIELD OF THE INVENTION

Described herein are methods for identifying and preparing high-affinity nucleic acid ligands to TGF β . The method utilized herein for identifying such nucleic acid ligands is called SELEX, an acronym for Systematic Evolution of Ligands by EXponential enrichment. This invention includes high affinity nucleic acid ligands of TGF β . Further disclosed are RNA ligands to TGF β 1. Also included are oligonucleotides containing nucleotide derivatives chemically modified at the 2'-positions of pyrimidines. Additionally disclosed are RNA ligands to TGF β 1 containing 2'-F-modifications. This invention also includes high affinity nucleic acid inhibitors of TGF β 1. The oligonucleotides of the present invention are useful as pharmaceuticals or diagnostic agents.

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BACKGROUND OF THE INVENTION

The transforming growth factor - β (TGF β) polypeptides influence growth, differentiation, and gene expression in many cell types. The first polypeptide of this family that was characterized, TGF β 1 has two identical 112 amino acid subunits which are covalently linked. TGF β 1 is a highly conserved protein with only a single amino acid difference distinguishing humans from mice. There are two other members of the TGF β gene family that are expressed in mammals. TGF β 2 is 71% homologous to TGF β 1 (de Martin *et al.* (1987) EMBO J. 6:3673-3677), whereas TGF β 3 is 80% homologous to TGF β 1 (Derynck *et al.* (1988) EMBO J 7:3737-3743). The structural characteristics of TGF β 1 as determined by nuclear magnetic resonance (Archer *et al.* (1993) Biochemistry 32:1164-1171) agree with the crystal structure of TGF β 2 (Daopin *et al.* (1992) Science 257:369-374; Schlunegger and Grutter (1992) Nature 358:430-434).

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Even though the TGF β 's have similar three dimensional structures, they are by no means physiologically equivalent. There are at least three different extracellular receptors, type I, II and III, involved in transmembrane signaling of TGF β to cells carrying the receptors. (For reviews, see Derynck (1994) TIBS 19:548-553 and Massague (1990) Ann.

Rev. Cell Biol. 6:597-641). In order for TGF β 2 to effectively interact with the type II TGF β receptor, the type III receptor must also be present (Derynck (1994) TIBS 19:548-553).

Vascular endothelial cells lack the type III receptor. Instead endothelial cells express a structurally related protein called endoglin (Cheifetz *et al.* (1992) J. Biol. Chem. 267:19027-19030), which only binds TGF β 1 and TGF β 3 with high affinity. Thus, the relative potency of the TGF β 's reflect the type of receptor expressed in a cell and organ system.

In addition to the regulation of the components in the multifactorial signaling pathway, the distribution of the synthesis of TGF β polypeptides also affects physiological function. The distribution of TGF β 2 and TGF β 3 is more limited (Derynck *et al.* (1988) EMBO J 7:3737-3743) than TGF β 1, e.g., TGF β 3 is limited to tissues of mesenchymal origin, whereas TGF β 1 is present in both tissues of mesenchymal and epithelial origin.

TGF β 1 is a multifunctional cytokine critical for tissue repair. High concentrations of TGF β 1 are delivered to the site of injury by platelet granules (Assoian and Sporn (1986) J. Cell Biol. 102:1217-1223). TGF β 1 initiates a series of events that promote healing including chemotaxis of cells such as leukocytes, monocytes and fibroblasts, and regulation of growth factors and cytokines involved in angiogenesis, cell division associated with tissue repair and inflammatory responses. TGF β 1 also stimulates the synthesis of extracellular matrix components (Roberts *et al.* (1986) Proc. Natl. Acad. Sci. USA 83:4167-4171; Sporn *et al.* (1983) Science 219:1329-1330; Massague (1987) Cell 49:437-438) and most importantly for understanding the pathophysiology of TGF β 1, TGF β 1 autoregulates its own synthesis (Kim *et al.* (1989) J. Biol. Chem. 264:7041-7045).

A number of diseases have been associated with TGF β 1 overproduction. Fibrotic diseases associated with TGF β 1 overproduction can be divided into chronic conditions such as fibrosis of the kidney, lung and liver and more acute conditions such as dermal scarring and restenosis. Synthesis and secretion of TGF β 1 by tumor cells can also lead to immune suppression such as seen in patients with aggressive brain or breast tumors (Arteaga *et al.* (1993) J. Clin. Invest. 92:2569-2576). The course of Leishmanial infection in mice is drastically altered by TGF β 1 (Barral-Netto *et al.* (1992) Science 257:545-547). TGF β 1 exacerbated the disease, whereas TGF β 1 antibodies halted the progression of the disease in genetically susceptible mice. Genetically resistant mice became susceptible to Leishmanial infection upon administration of TGF β 1.

The profound effects of TGF β 1 on extracellular matrix deposition have been reviewed (Rocco and Ziyadeh (1991) in Contemporary Issues in Nephrology v.23, "Hormones, Autocoids and the Kidney," ed. Jay Stein, Churchill Livingston, NY pp.391-410; Roberts *et al.* (1988) *Rec. Prog. Hormone Res.* 44:157-197) and include the stimulation of the synthesis and the inhibition of degradation of extracellular matrix components. Since the structure and filtration properties of the glomerulus are largely determined by the extracellular matrix composition of the mesangium and glomerular membrane, it is not surprising that TGF β 1 has profound effects on the kidney. The accumulation of mesangial matrix in proliferative glomerulonephritis (Border *et al.* (1990) *Kidney Int.* 37:689-695) and diabetic nephropathy (Mauer *et al.* (1984) *J. Clin. Invest.* 74:1143-1155) are clear and dominant pathological features of the diseases. TGF β 1 levels are elevated in human diabetic glomerulosclerosis (advanced neuropathy) (Yamamoto *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:1814-1818). TGF β 1 is an important mediator in the genesis of renal fibrosis in a number of animal models (Phan *et al.* (1990) *Kidney Int.* 37:426; Okuda *et al.* (1990) *J. Clin. Invest.* 86:453). Suppression of experimentally induced glomerulonephritis in rats has been demonstrated by antiserum against TGF β 1 (Border *et al.* (1990) *Nature* 346:371) and by an extracellular matrix protein, decorin, which can bind TGF β 1 (Border *et al.* (1992) *Nature* 360:361-363).

Too much TGF β 1 leads to dermal scar-tissue formation. Neutralizing TGF β 1 antibodies injected into the margins of healing wounds in rats have been shown to inhibit scarring without interfering with the rate of wound healing or the tensile strength of the wound (Shah *et al.* (1992) *Lancet* 339:213-214). At the same time there was reduced angiogenesis, reduced number of macrophages and monocytes in the wound, and a reduced amount of disorganized collagen fiber deposition in the scar tissue.

TGF β 1 may be a factor in the progressive thickening of the arterial wall which results from the proliferation of smooth muscle cells and deposition of extracellular matrix in the artery after balloon angioplasty. The diameter of the restenosed artery may be reduced 90% by this thickening, and since most of the reduction in diameter is due to extracellular matrix rather than smooth muscle cell bodies, it may be possible to open these vessels to 50% simply by reducing extensive extracellular matrix deposition. In uninjured pig arteries transfected *in vivo* with a TGF β 1 gene, TGF β 1 gene expression was associated with both extracellular matrix synthesis and hyperplasia (Nabel *et al.* (1993) *Proc. Natl.*

Acad. Sci. USA 90:10759-10763). The TGF β 1 induced hyperplasia was not as extensive as that induced with PDGF-BB, but the extracellular matrix was more extensive with TGF β 1 transfectants. No extracellular matrix deposition was associated with FGF-1 (a secreted form of FGF) induced hyperplasia in this gene transfer pig model (Nabel (1993) Nature 362:844-846).

There are several types of cancer where TGF β 1 produced by the tumor may be deleterious. MATLyLu rat cancer cells (Steiner and Barrack (1992) Mol. Endocrinol. 6:15-25) and MCF-7 human breast cancer cells (Arteaga *et al.* (1993) Cell Growth and Differ. 4:193-201) became more tumorigenic and metastatic after transfection with a vector expressing the mouse TGF β 1. In breast cancer, poor prognosis is associated with elevated TGF β (Dickson *et al.* (1987) Proc. Natl. Acad. Sci. USA 84:837-841; Kasid *et al.* (1987) Cancer Res. 47:5733-5738; Daly *et al.* (1990) J. Cell Biochem. 43:199-211; Barrett-Lee *et al.* (1990) Br. J Cancer 61:612-617; King *et al.* (1989) J. Steroid Biochem. 34:133-138; Welch *et al.* (1990) Proc. Natl. Acad. Sci. USA 87:7678-7682; Walker *et al.* (1992) Eur. J. Cancer 238:641-644) and induction of TGF β 1 by tamoxifen treatment (Butta *et al.* (1992) Cancer Res. 52:4261-4264) has been associated with failure of tamoxifen treatment for breast cancer (Thompson *et al.* (1991) Br. J Cancer 63:609-614). Anti TGF β 1 antibodies inhibit the growth of MDA-231 human breast cancer cells in athymic mice (Arteaga *et al.* (1993) J. Clin. Invest. 92:2569-2576), a treatment which is correlated with an increase in spleen natural killer cell activity. CHO cells transfected with latent TGF β 1 also showed decreased NK activity and increased tumor growth in nude mice (Wallick *et al.* (1990) J. Exp. Med. 172:1777-1784). Thus, TGF β 1 secreted by breast tumors may cause an endocrine immune suppression.

High plasma concentrations of TGF β 1 have been shown to indicate poor prognosis for advanced breast cancer patients (Anscher *et al.* (1993) N. Engl. J. Med. 328:1592-1598). Patients with high circulating TGF β before high dose chemotherapy and autologous bone marrow transplantation are at high risk for hepatic veno-occlusive disease (15-50% of all patients with a mortality rate up to 50%) and idiopathic interstitial pneumonitis (40-60% of all patients). The implication of these findings is 1) that elevated plasma levels of TGF β 1 can be used to identify at risk patients and 2) that reduction of TGF β 1 could decrease the morbidity and mortality of these common treatments for breast cancer patients.

A method for the *in vitro* evolution of nucleic acid molecules with high affinity

binding to target molecules has been developed. This method, Systematic Evolution of Ligands by EXponential enrichment, termed SELEX, is described in United States Patent Application Serial No. 07/536,428, filed June 11, 1990, entitled "Systematic Evolution of Ligands by Exponential Enrichment," now abandoned, United States Patent Application
5 Serial No. 07/714,131, filed June 10, 1991, entitled "Nucleic Acid Ligands," now issued as United States Patent No. 5,475,096, United States Patent Application Serial No. 07/931,473, filed August 17, 1992, entitled "Methods for Identifying Nucleic Acid Ligands," now United States Patent No. 5,270,163 (see also WO91/19813), each of which is herein specifically incorporated by reference. Each of these applications, collectively referred to herein as the
10 SELEX Patent Applications, describe a fundamentally novel method for making a nucleic acid ligand to any desired target molecule.

The SELEX method involves selection from a mixture of candidate oligonucleotides and step-wise iterations of binding, partitioning and amplification, using the same general selection theme, to achieve virtually any desired criterion of binding affinity and selectivity.
15 Starting from a mixture of nucleic acids, preferably comprising a segment of randomized sequence, the SELEX method includes steps of contacting the mixture with the target under conditions favorable for binding, partitioning unbound nucleic acids from those nucleic acids which have bound to target molecules, dissociating the nucleic acid-target complexes, amplifying the nucleic acids dissociated from the nucleic acid-target complexes to yield a
20 ligand-enriched mixture of nucleic acids, then reiterating the steps of binding, partitioning, dissociating and amplifying through as many cycles as desired to yield high affinity nucleic acid ligands to the target molecule.

The basic SELEX method may be modified to achieve specific objectives. For example, United States Patent Application Serial No. 07/960,093, filed October 14, 1992,
25 entitled "Method for Selecting Nucleic Acids on the Basis of Structure," now abandoned, describes the use of SELEX in conjunction with gel electrophoresis to select nucleic acid molecules with specific structural characteristics, such as bent DNA. (See United States Patent No. 5,707,796). United States Patent Application Serial No. 08/123,935, filed September 17, 1993, entitled "Photoselection of Nucleic Acid Ligands," now abandoned,
30 describes a SELEX based method for selecting nucleic acid ligands containing photoreactive groups capable of binding and/or photocrosslinking to and/or photoinactivating a target molecule. (See United States Patent No. 5,763,177). United States Patent Application

Serial No. 08/134,028, filed October 7, 1993, entitled "High-Affinity Nucleic Acid Ligands That Discriminate Between Theophylline and Caffeine," abandoned in favor of United States Patent Application Serial No. 08/443,957, now United States Patent No. 5,580,737, describes a method for identifying highly specific nucleic acid ligands able to discriminate
5 between closely related molecules, termed "Counter-SELEX." United States Patent Application Serial No. 08/143,564, filed October 25, 1993, entitled "Systematic Evolution of Ligands by EXponential Enrichment: Solution SELEX," abandoned in favor of United States Patent Application Serial No. 08/461,061, now United States Patent No. 5,567,588) and United States Patent Application Serial No. 08/792,075, filed January 31, 1997, entitled
10 "Flow Cell SELEX," now United States Patent No. 5,861,254, describe SELEX-based methods which achieve highly efficient partitioning between oligonucleotides having high and low affinity for a target molecule. United States Patent Application Serial No. 07/964,624, filed October 21, 1992, entitled "Nucleic Acid Ligands to HIV-RT and HIV-1 Rev," now United States Patent No. 5,496,938, describes methods for obtaining improved
15 Nucleic Acid Ligands after the SELEX process has been performed. United States Patent Application Serial No. 08/400,440, filed March 8, 1995, entitled "Systematic Evolution of Ligands by EXponential Enrichment: Chemi-SELEX," now United States Patent No. 5,705,337, describes methods for covalently linking a ligand to its target.

The SELEX method encompasses the identification of high-affinity nucleic acid
20 ligands containing modified nucleotides conferring improved characteristics on the ligand, such as improved *in vivo* stability or delivery. Examples of such modifications include chemical substitutions at the ribose and/or phosphate and/or base positions. Specific SELEX-identified nucleic acid ligands containing modified nucleotides are described in United States Patent Application Serial No. 08/117,991, filed September 8, 1993, entitled
25 "High Affinity Nucleic Acid Ligands Containing Modified Nucleotides," abandoned in favor of United States Patent Application Serial No. 08/430,709, now United States Patent No. 5,660,985, that describes oligonucleotides containing nucleotide derivatives chemically modified at the 5- and 2'-positions of pyrimidines, as well as specific RNA ligands to thrombin containing 2'-amino modifications. United States Patent Application Serial No.
30 08/134,028, *supra*, describes highly specific nucleic acid ligands containing one or more nucleotides modified with 2'-amino (2'-NH₂), 2'-fluoro (2'-F), and/or 2'-O-methyl (2'-OMe). United States Patent Application Serial No. 08/264,029, filed June 22, 1994, entitled

"Novel Method of Preparation of Known and Novel 2' Modified Nucleosides by Intramolecular Nucleophilic Displacement," describes oligonucleotides containing various 2'-modified pyrimidines. International Publication No. WO 98/30720, published July 16, 1998, entitled "Bioconjugation of Oligonucleotides," describes a method for identifying
5 bioconjugates to a target comprising nucleic acid ligands derivatized with a molecular entity exclusively at the 5'-position of the nucleic acid ligands.

The SELEX method encompasses combining selected oligonucleotides with other selected oligonucleotides and non-oligonucleotide functional units as described in United States Patent Application Serial No. 08/284,063, filed August 2, 1994, entitled "Systematic
10 Evolution of Ligands by Exponential Enrichment: Chimeric SELEX," now United States Patent No. 5,637,459 and United States Patent Application Serial No. 08/234,997, filed April 28, 1994, entitled "Systematic Evolution of Ligands by Exponential Enrichment: Blended SELEX," now United States Patent No. 5,683,867, respectively. These applications allow the combination of the broad array of shapes and other properties, and the
15 efficient amplification and replication properties of oligonucleotides with the desirable properties of other molecules. The full text of the above described patent applications, including but not limited to, all definitions and descriptions of the SELEX process, are specifically incorporated herein by reference in their entirety.

20 BRIEF SUMMARY OF THE INVENTION

The present invention includes methods of identifying and producing nucleic acid ligands to transforming growth factor beta (TGF β) and the nucleic acid ligands so identified and produced. For the purpose of this application, TGF β includes human TGF β 1, TGF β 2, TGF β 3 and TGF β 's that are substantially homologous thereto. By substantially homologous
25 it is meant a degree of amino acid sequence identity of 70% or more. In particular, RNA sequences are provided that are capable of binding specifically to TGF β 1. Specifically included in the invention are the RNA ligand sequences shown in Table 3 (SEQ ID NOS:6-143). Also included in this invention are RNA ligands of TGF β 1 that inhibit the function of TGF β 1.

30 Further included in this invention is a method of identifying nucleic acid ligands and nucleic acid ligand sequences to TGF β comprising the steps of (a) preparing a candidate mixture of nucleic acids, (b) contacting the candidate mixture of nucleic acids with TGF β ,

(c) partitioning between members of said candidate mixture on the basis of affinity to TGF β , and (d) amplifying the selected molecules to yield a mixture of nucleic acids enriched for nucleic acid sequences with a relatively higher affinity for binding to TGF β .

More specifically, the present invention includes the RNA ligands to TGF β identified according to the above-described method, including those ligands shown in Table 3 (SEQ ID NOS:6-143). Also included are nucleic acid ligands to TGF β that are substantially homologous to any of the given ligands and that have substantially the same ability to bind TGF β and inhibit the function of TGF β . Further included in this invention are nucleic acid ligands to TGF β that have substantially the same structural form as the ligands presented herein and that have substantially the same ability to bind TGF β and inhibit the function of TGF β .

The present invention also includes other modified nucleotide sequences based on the nucleic acid ligands identified herein and mixtures of the same.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A and 1B show the binding curves of rounds 0 (\circ), 14 (\blacktriangle), 15 (\blacksquare) and 16 (\bullet) of the 40N pool (Fig. 1A) and rounds 0 (\circ), 14 (\blacksquare), 15 (\blacktriangle) and 17 (\bullet) of the 30N pool (Fig. 1B) presented as %RNA bound vs. concentration of TGF β 1.

Figure 2 shows the affinity sensorgram of random RNA (\diamond), ligand 40-03 (\circ), ligand 40-60 (\blacktriangle) and polyclonal anti TGF β 1 antibody (\bullet) performed on TGF β 1, expressed as response units vs. time.

Figures 3A-3C show sensorgrams obtained in a binding specificity analysis of TGF β 1 performed on random RNA (Fig. 3A), ligand 40-03 (Fig. 3B) and ligand 40-60 (Fig. 3C) with various concentrations of TGF β 1, expressed as response units vs. time. Figures 3D-3F show sensorgrams obtained in a binding specificity analysis of TGF β 2 performed on random RNA (Fig. 3D), ligand 40-03 (Fig. 3E) and ligand 40-60 (Fig. 3F) with various concentrations of TGF β 2, expressed as response units vs. time.

Figures 4A and 4B illustrate the results of the TGF β 1 bioassay on mink lung epithelial cells (MLEC). Figures 4A and 4B show the inhibitory activity of rounds 11 (\blacksquare) and 14 (\bullet) of the 40N pool (Fig. 4A) and rounds 11 (\blacksquare) and 14 (\bullet) of the 30N pool (Fig. 4B) compared to random RNA (\blacktriangle). The results are expressed as ^3H -thymidine incorporation as

net % of control vs. concentration of TGF β 1, where control is the amount of ^3H -thymidine incorporation in the absence of TGF β 1 and RNA minus the amount of incorporation in the presence of TGF β 1 alone.

Figures 5A-5D illustrate the results of the TGF β 1 bioassay on mink lung epithelial cells (MLEC). Figure 5A is a TGF β 1 titration curve presented as ^3H -thymidine incorporation as a per cent of control vs. concentration of TGF β 1. Figures 5B-5D illustrate the bioactivities of round 16 of the 40N pool (Fig. 5B, (●)), ligand 40-03 (Fig. 5C, (●)) and ligand 40-60 (Fig. 5D, (●)) as compared to the bioactivities of a polyclonal anti-TGF β 1 antibody (○) and random RNA (■), presented as ^3H -thymidine incorporation as a per cent of control vs. concentration of TGF β 1.

Figure 6 shows the bioactivities of random RNA (■), ligand 40-60 (▲), ligand 40-03 (●), a monoclonal antibody specific for TGF β 2 and TGF β 3 (○) and a pan-specific antibody specific for TGF β 1, TGF β 2 and TGF β 3 (Δ), presented as ^3H -thymidine incorporation as a per cent of control vs. concentration of TGF β 1.

Figure 7 is a proposed folding of the class 1 bioactive ligands. S1, S2 and S3 designate stem 1, stem 2 and stem 3 of the proposed structure.

DETAILED DESCRIPTION OF THE INVENTION

This application describes high-affinity nucleic acid ligands to TGF β identified through the method known as SELEX. SELEX is described in United States Patent Application Serial No. 07/536,428, entitled "Systematic Evolution of Ligands by EXponential Enrichment," now abandoned, United States Patent Application Serial No. 07/714,131, filed June 10, 1991, entitled "Nucleic Acid Ligands," now United States Patent No. 5,475,096, United States Patent Application Serial No. 07/931,473, filed August 17, 1992, entitled "Methods for Identifying Nucleic Acid Ligands," now United States Patent No. 5,270,163, (see also WO91/19813). These applications, each specifically incorporated herein by reference, are collectively called the SELEX Patent Applications. Certain terms used to described the invention herein are defined as follows.

"Nucleic Acid Ligand" as used herein is a non-naturally occurring nucleic acid having a desirable action on a target. A desirable action includes, but is not limited to, binding of the target, catalytically changing the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target, covalently attaching

to the target as in a suicide inhibitor, and facilitating the reaction between the target and another molecule. In the preferred embodiment, the desirable action is specific binding to a target molecule, such target molecule being a three dimensional chemical structure other than a polynucleotide that binds to the nucleic acid ligand through a mechanism which predominantly depends on Watson/Crick base pairing or triple helix binding, wherein the nucleic acid ligand is not a nucleic acid having the known physiological function of being bound by the target molecule. Nucleic acid ligands include nucleic acids that are identified from a candidate mixture of nucleic acids, said nucleic acid ligand being a ligand of a given target by the method comprising: a) contacting the candidate mixture with the target, wherein nucleic acids having an increased affinity to the target relative to the candidate mixture may be partitioned from the remainder of the candidate mixture; b) partitioning the increased affinity nucleic acids from the remainder of the candidate mixture; and c) amplifying the increased affinity nucleic acids to yield a ligand-enriched mixture of nucleic acids.

"Candidate Mixture" is a mixture of nucleic acids of differing sequence from which to select a desired ligand. The source of a candidate mixture can be from naturally-occurring nucleic acids or fragments thereof, chemically synthesized nucleic acids, enzymatically synthesized nucleic acids or nucleic acids made by a combination of the foregoing techniques. In a preferred embodiment, each nucleic acid has fixed sequences surrounding a randomized region to facilitate the amplification process.

"Nucleic Acid" means either DNA, RNA, single-stranded or double-stranded and any chemical modifications thereof. Modifications include, but are not limited to, those which provide other chemical groups that incorporate additional charge, polarizability, hydrogen bonding, electrostatic interaction, and fluxionality to the nucleic acid ligand bases or to the nucleic acid ligand as a whole. Such modifications include, but are not limited to, 2'-position sugar modifications, 5-position pyrimidine modifications, 8-position purine modifications, modifications at exocyclic amines, substitution of 4-thiouridine, substitution of 5-bromo or 5-iodo-uracil, backbone modifications, methylations, unusual base-pairing combinations such as the isobases isocytidine and isoguanidine and the like. Modifications can also include 3' and 5' modifications such as capping.

"SELEX" methodology involves the combination of selection of nucleic acid ligands which interact with a target in a desirable manner, for example binding to a protein, with

amplification of those selected nucleic acids. Iterative cycling of the selection/amplification steps allows selection of one or a small number of nucleic acids which interact most strongly with the target from a pool which contains a very large number of nucleic acids. Cycling of the selection/amplification procedure is continued until a selected goal is achieved. In the present invention, the SELEX methodology is employed to obtain nucleic acid ligands to TGF β . The SELEX methodology is described in the SELEX Patent Applications.

"Target" means any compound or molecule of interest for which a ligand is desired. A target can be a protein, peptide, carbohydrate, polysaccharide, glycoprotein, hormone, receptor, antigen, antibody, virus, substrate, metabolite, transition state analog, cofactor, inhibitor, drug, dye, nutrient, growth factor, etc. without limitation. In this application, the target is a TGF β , preferably TGF β 1.

In its most basic form, the SELEX process may be defined by the following series of steps.

1) A candidate mixture of nucleic acids of differing sequence is prepared. The candidate mixture generally includes regions of fixed sequences (i.e., each of the members of the candidate mixture contains the same sequences in the same location) and regions of randomized sequences. The fixed sequence regions are selected either: (a) to assist in the amplification steps described below, (b) to mimic a sequence known to bind to the target, or (c) to enhance the concentration of a given structural arrangement of the nucleic acids in the candidate mixture. The randomized sequences can be totally randomized (i.e., the probability of finding a base at any position being one in four) or only partially randomized (e.g., the probability of finding a base at any location can be selected at any level between 0 and 100 percent).

2) The candidate mixture is contacted with the selected target under conditions favorable for binding between the target and members of the candidate mixture. Under these circumstances, the interaction between the target and the nucleic acids of the candidate mixture can be considered as forming nucleic acid-target pairs between the target and those nucleic acids having the strongest affinity for the target.

3) The nucleic acids with the highest affinity for the target are partitioned from those nucleic acids with lesser affinity to the target. Because only an extremely small number of sequences (and possibly only one molecule of nucleic acid) corresponding to the highest affinity nucleic acids exist in the candidate mixture, it is generally desirable to set the

partitioning criteria so that a significant amount of the nucleic acids in the candidate mixture (approximately 5-50%) are retained during partitioning.

4) Those nucleic acids selected during partitioning as having the relatively higher affinity to the target are then amplified to create a new candidate mixture that is enriched in nucleic acids having a relatively higher affinity for the target.

5) By repeating the partitioning and amplifying steps above, the newly formed candidate mixture contains fewer and fewer weakly binding sequences, and the average degree of affinity of the nucleic acids to the target will generally increase. Taken to its extreme, the SELEX process will yield a candidate mixture containing one or a small number of unique nucleic acids representing those nucleic acids from the original candidate mixture having the highest affinity to the target molecule.

The SELEX Patent Applications describe and elaborate on this process in great detail. Included are targets that can be used in the process; methods for partitioning nucleic acids within a candidate mixture; and methods for amplifying partitioned nucleic acids to generate enriched candidate mixture. The SELEX Patent Applications also describe ligands obtained to a number of target species, including both protein targets where the protein is and is not a nucleic acid binding protein.

The SELEX method further encompasses combining selected nucleic acid ligands with lipophilic or non-immunogenic, high molecular weight compounds in a diagnostic or therapeutic complex as described in United States Patent Application No. 08/434,465, filed May 4, 1995, entitled "Nucleic Acid Ligand Complexes." VEGF nucleic acid ligands that are associated with a lipophilic compound, such as diacyl glycerol or dialkyl glycerol, in a diagnostic or therapeutic complex are described in United States Patent Application Serial No. 08/739,109, filed October 25, 1996, entitled "Vascular Endothelial Growth Factor (VEGF) Nucleic Acid Ligand Complexes," now United States Patent No. 5,859,228. VEGF nucleic acid ligands that are associated with a lipophilic compound, such as a glycerol lipid, or a non-immunogenic, high molecular weight compound, such as polyalkylene glycol, are further described in United States Patent Application Serial No. 08/897,351, filed July 21, 1997, entitled "Vascular Endothelial Growth Factor (VEGF) Nucleic Acid Ligand Complexes." VEGF nucleic acid ligands that are associated with a non-immunogenic, high molecular weight compound or lipophilic compound are also further described in WO 98/18480, published May 7, 1998, entitled "Vascular Endothelial Growth Factor (VEGF) Nucleic Acid

Ligand Complexes." Each of the above described patent applications which describe modifications of the basic SELEX procedure are specifically incorporated by reference herein in their entirety.

Certain embodiments of the present invention provide a complex comprising one or
5 more nucleic acid ligands to TGF β covalently linked with a non-immunogenic, high molecular weight compound or lipophilic compound. A complex as used herein describes the molecular entity formed by the covalent linking of the nucleic acid ligand of TGF β to a non-immunogenic, high molecular weight compound. A non-immunogenic, high molecular weight compound is a compound between approximately 100 Da to 1,000,000 Da, more
10 preferably approximately 1000 Da to 500,000 Da, and most preferably approximately 1000 Da to 200,000 Da, that typically does not generate an immunogenic response. For the purposes of this invention, an immunogenic response is one that causes the organism to make antibody proteins. In a preferred embodiment of the invention, the non-immunogenic, high molecular weight compound is a polyalkylene glycol. In the most preferred embodiment, the
15 polyalkylene glycol is polyethylene glycol (PEG). More preferably, the PEG has a molecular weight of about 10-80K. Most preferably, the PEG has a molecular weight of about 20-45K. In certain embodiments of the invention, the non-immunogenic, high molecular weight compound can also be a nucleic acid ligand.

Another embodiment of the invention is directed to complexes comprised of a nucleic
20 acid ligand to TGF β and a lipophilic compound. Lipophilic compounds are compounds that have the propensity to associate with or partition into lipids and/or other materials or phases with low dielectric constants, including structures that are comprised substantially of lipophilic components. Lipophilic compounds include lipids as well as non-lipid containing compounds that have the propensity to associate with lipids (and/or other materials or phases with low
25 dielectric constants). Cholesterol, phospholipid and glycerol lipids, such as dialkylglycerol, diacylglycerol, and glycerol amide lipids are further examples of lipophilic compounds. In a preferred embodiment, the lipophilic compound is a glycerol lipid.

The non-immunogenic, high molecular weight compound or lipophilic compound may be covalently bound to a variety of positions on the nucleic acid ligand to TGF β , such as to an
30 exocyclic amino group on the base, the 5-position of a pyrimidine nucleotide, the 8-position of a purine nucleotide, the hydroxyl group of the phosphate, or a hydroxyl group or other group at the 5' or 3' terminus of the nucleic acid ligand to TGF β . In embodiments where the lipophilic

compound is a glycerol lipid, or the non-immunogenic, high molecular weight compound is polyalkylene glycol or polyethylene glycol, preferably the non-immunogenic, high molecular weight compound is bonded to the 5' or 3' hydroxyl of the phosphate group thereof. In the most preferred embodiment, the lipophilic compound or non-immunogenic, high molecular weight compound is bonded to the 5' hydroxyl of the phosphate group of the nucleic acid ligand. Attachment of the non-immunogenic, high molecular weight compound or lipophilic compound to the nucleic acid ligand of TGF β can be done directly or with the utilization of linkers or spacers.

A linker is a molecular entity that connects two or more molecular entities through covalent bonds or non-covalent interactions, and can allow spatial separation of the molecular entities in a manner that preserves the functional properties of one or more of the molecular entities. A linker can also be referred to as a spacer.

The complex comprising a nucleic acid ligand to TGF β and a non-immunogenic, high molecular weight compound or lipophilic compound can be further associated with a lipid construct. Lipid constructs are structures containing lipids, phospholipids, or derivatives thereof comprising a variety of different structural arrangements which lipids are known to adopt in aqueous suspension. These structures include, but are not limited to, lipid bilayer vesicles, micelles, liposomes, emulsions, lipid ribbons or sheets, and may be complexed with a variety of drugs and components which are known to be pharmaceutically acceptable. In the preferred embodiment, the lipid construct is a liposome. The preferred liposome is unilamellar and has a relative size less than 200 nm. Common additional components in lipid constructs include cholesterol and alpha-tocopherol, among others. The lipid constructs may be used alone or in any combination which one skilled in the art would appreciate to provide the characteristics desired for a particular application. In addition, the technical aspects of lipid constructs and liposome formation are well known in the art and any of the methods commonly practiced in the field may be used for the present invention.

The SELEX method further comprises identifying bioconjugates to a target. Copending International Publication No. WO 98/30720, published July 6, 1998, entitled "Bioconjugation of Oligonucleotides," describes a method for enzymatically synthesizing bioconjugates comprising RNA derivatized exclusively at the 5'-position with a molecular entity, and a method for identifying bioconjugates to a target comprising nucleic acid ligands derivatized with a molecular entity exclusively at the 5'-position of the nucleic acid

ligands. A bioconjugate as used herein refers to any oligonucleotide which has been derivatized with another molecular entity. In the preferred embodiment, the molecular entity is a macromolecule. As used herein, a macromolecule refers to a large organic molecule. Examples of macromolecules include, but are not limited to nucleic acids, oligonucleotides, proteins, peptides, carbohydrates, polysaccharides, glycoproteins, lipophilic compounds, such as cholesterol, phospholipids, diacyl glycerols and dialkyl glycerols, hormones, drugs, non-immunogenic high molecular weight compounds, fluorescent, chemiluminescent and bioluminescent marker compounds, antibodies and biotin, etc. without limitation. In certain embodiments, the molecular entity may provide certain desirable characteristics to the nucleic acid ligand, such as increasing RNA hydrophobicity and enhancing binding, membrane partitioning and/or permeability. Additionally, reporter molecules, such as biotin, fluorescein or peptidyl metal chelates for incorporation of diagnostic radionuclides may be added, thus providing a bioconjugate which may be used as a diagnostic agent.

Certain embodiments of the present invention provide bioconjugates to TGF β comprising RNA derivatized exclusively at the 5'-position with a molecular entity obtained by the enzymatic method described in WO 98/30720. Other embodiments of the present invention provide bioconjugates to TGF β comprising a nucleic acid ligand covalently bonded to a macromolecule, obtained from a candidate mixture of bioconjugates, obtained by the method described in WO 98/30720.

The methods described herein and the nucleic acid ligands identified by such methods are useful for both therapeutic and diagnostic purposes. Therapeutic uses include the treatment or prevention of diseases or medical conditions in human patients. Therapeutic uses may also include veterinary applications.

Diagnostic utilization may include both *in vivo* or *in vitro* diagnostic applications. The SELEX method generally, and the specific adaptations of the SELEX method taught and claimed herein specifically, are particularly suited for diagnostic applications. SELEX identifies nucleic acid ligands that are able to bind targets with high affinity and with surprising specificity. These characteristics are, of course, the desired properties one skilled in the art would seek in a diagnostic ligand.

The nucleic acid ligands of the present invention may be routinely adapted for diagnostic purposes according to any number of techniques employed by those skilled in the

art or by the methods described in WO 98/30720, *supra*. Diagnostic agents need only be able to allow the user to identify the presence of a given target at a particular locale or concentration. Simply the ability to form binding pairs with the target may be sufficient to trigger a positive signal for diagnostic purposes. Those skilled in the art would also be able to adapt any nucleic acid ligand by procedures known in the art to incorporate a labeling tag in order to track the presence of such ligand. Such a tag could be used in a number of diagnostic procedures. The nucleic acid ligands to TGF β described herein may specifically be used for identification of the TGF β protein.

SELEX provides high affinity ligands of a target molecule. This represents a singular achievement that is unprecedented in the field of nucleic acids research. The present invention applies the SELEX procedure to the specific target of TGF β 1. In the Example section below, the experimental parameters used to isolate and identify the nucleic acid ligands to TGF β 1 are described.

In order to produce nucleic acids desirable for use as a pharmaceutical, it is preferred that the nucleic acid ligand (1) binds to the target in a manner capable of achieving the desired effect on the target; (2) be as small as possible to obtain the desired effect; (3) be as stable as possible; and (4) be a specific ligand to the chosen target. In most situations, it is preferred that the nucleic acid ligand have the highest possible affinity to the target.

In the present invention, SELEX experiments were performed in order to identify RNA ligands with specific high affinity for TGF β 1 from degenerate libraries containing 20, 30 or 40 random positions (20N7 (SEQ ID NO:1), 30N7 (SEQ ID NO:2) or 40N7 (SEQ ID NO:3)) (Table 1). This invention includes the specific RNA ligands to TGF β 1 shown in Table 3 (SEQ ID NOS:6-143), identified by the methods described in Examples 1 and 2. This invention further includes RNA ligands to TGF β 1 which inhibit TGF β 1 function, presumably by inhibiting the interaction of TGF β 1 with its receptor. The scope of the ligands covered by this invention extends to all nucleic acid ligands of TGF β , modified and unmodified, identified according to the SELEX procedure. More specifically, this invention includes nucleic acid sequences that are substantially homologous to the ligands shown in Table 3 (SEQ ID NOS:6-143). By substantially homologous it is meant a degree of primary sequence homology in excess of 70%, most preferably in excess of 80%, and even more preferably in excess of 90%, 95% or 99%. The percentage of homology as described herein is calculated as the percentage of nucleotides found in the smaller of the two sequences

which align with identical nucleotide residues in the sequence being compared when 1 gap in a length of 10 nucleotides may be introduced to assist in that alignment. A review of the sequence homologies of the ligands of TGF β shown in Tables 3 (SEQ ID NOS:6-143) shows that some sequences with little or no primary homology may have substantially the same ability to bind TGF β . For this reason, this invention also includes nucleic acid ligands that have substantially the same structure and ability to bind TGF β as the nucleic acid ligands shown in Table 3 (SEQ ID NOS:6-143). Substantially the same ability to bind TGF β means that the affinity is within one or two orders of magnitude of the affinity of the ligands described herein. It is well within the skill of those of ordinary skill in the art to determine whether a given sequence -- substantially homologous to those specifically described herein -- has substantially the same ability to bind TGF β .

This invention also includes nucleic acid ligands that have substantially the same postulated structure or structural motifs. Substantially the same structure or structural motifs can be postulated by sequence alignment using the Zukerfold program (see Zuker (1989) Science 244:48-52) as would be known in the art, other computer programs can be used for predicting secondary structure and structural motifs. Substantially the same structure or structural motif of nucleic acid ligands in solution or as a bound structure can also be postulated using NMR or other techniques as would be known in the art.

One potential problem encountered in the therapeutic, prophylactic, and *in vivo* diagnostic use of nucleic acids is that oligonucleotides in their phosphodiester form may be quickly degraded in body fluids by intracellular and extracellular enzymes such as endonucleases and exonucleases before the desired effect is manifest. Certain chemical modifications of the nucleic acid ligand can be made to increase the *in vivo* stability of the nucleic acid ligand or to enhance or to mediate the delivery of the nucleic acid ligand. See, e.g., United States Patent Application Serial No. 08/117,991, filed September 8, 1993, entitled "High Affinity Nucleic Acid Ligands Containing Modified Nucleotides," abandoned in favor of United States Patent Application Serial No. 08/430,709, now issued as United States Patent No. 5,660,985 and United States Patent Application Serial No. 08/434,465, filed May 4, 1995, entitled "Nucleic Acid Ligand Complexes," which are specifically incorporated herein by reference. Modifications of the nucleic acid ligands contemplated in this invention include, but are not limited to, those which provide other chemical groups that incorporate additional charge, polarizability, hydrophobicity, hydrogen bonding,

electrostatic interaction, and fluxionality to the nucleic acid ligand bases or to the nucleic acid ligand as a whole. Such modifications include, but are not limited to, 2'-position sugar modifications, 5-position pyrimidine modifications, 8-position purine modifications, modifications at exocyclic amines, substitution of 4-thiouridine, substitution of 5-bromo or 5-iodo-uracil, backbone modifications, phosphorothioate or alkyl phosphate modifications, methylations, unusual base-pairing combinations such as the isobases isocytidine and isoguanidine and the like. Modifications can also include 3' and 5' modifications such as capping.

Where the nucleic acid ligands are derived by the SELEX method, the modifications can be pre- or post- SELEX modifications. Pre-SELEX modifications yield nucleic acid ligands with both specificity for their SELEX target and improved *in vivo* stability. Post-SELEX modifications made to 2'-OH nucleic acid ligands can result in improved *in vivo* stability without adversely affecting the binding capacity of the nucleic acid ligand. The preferred modifications of the nucleic acid ligands of the subject invention are 5' and 3' phosphorothioate capping and/or 3'-3' inverted phosphodiester linkage at the 3' end. In one preferred embodiment, the preferred modification of the nucleic acid ligand is a 3'-3' inverted phosphodiester linkage at the 3' end. Additional 2'-fluoro (2'-F) and/or 2'-amino (2'-NH₂) and/or 2'-O methyl (2'-OMe) modification of some or all of the nucleotides is preferred. Described herein are nucleic acid ligands that were 2'-F modified and incorporated into the SELEX process. Other modifications are known to one of ordinary skill in the art. Such modifications may be made post-SELEX (modification of previously identified unmodified ligands) or by incorporation into the SELEX process.

As described above, because of their ability to selectively bind TGF β , the nucleic acid ligands to TGF β described herein are useful as pharmaceuticals. This invention, therefore, also includes a method for treating TGF β -mediated pathological conditions by administration of a nucleic acid ligand capable of binding to TGF β .

Therapeutic compositions of the nucleic acid ligands may be administered parenterally by injection, although other effective administration forms, such as intraarticular injection, inhalant mists, orally active formulations, transdermal iontophoresis or suppositories, are also envisioned. One preferred carrier is physiological saline solution, but it is contemplated that other pharmaceutically acceptable carriers may also be used. In one preferred embodiment, it is envisioned that the carrier and the ligand constitute a

physiologically-compatible, slow release formulation. The primary solvent in such a carrier may be either aqueous or non-aqueous in nature. In addition, the carrier may contain other pharmacologically-acceptable excipients for modifying or maintaining the pH, osmolarity, viscosity, clarity, color, sterility, stability, rate of dissolution, or odor of the formulation.

5 Similarly, the carrier may contain still other pharmacologically-acceptable excipients for modifying or maintaining the stability, rate of dissolution, release, or absorption of the ligand. Such excipients are those substances usually and customarily employed to formulate dosages for parental administration in either unit dose or multi-dose form.

10 Once the therapeutic composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready to use form or requiring reconstitution immediately prior to administration. The manner of administering formulations containing nucleic acid ligands for systemic delivery may be via subcutaneous, intramuscular, intravenous, intranasal or vaginal or rectal suppository.

15 The following Examples are provided to explain and illustrate the present invention and are not intended to be limiting of the invention. Example 1 describes the various materials and experimental procedures used in Example 2. Example 2 describes a representative method for identifying RNA ligands by the SELEX method which bind TGF β 1. Example 3 describes the affinities the ligands have for TGF β 1. Example 4
20 describes the specificity of ligands to hTGF β 1. Example 5 describes the inhibition of TGF β 1 bioactivity with several ligands. Example 6 summarizes the results of the data from Examples 2-5. Example 7 describes the proposed secondary structure of bioactive TGF β 1 ligands.

25 **EXAMPLES**

Example 1. Experimental Procedures

a) Materials

30 Recombinant human Transforming Growth Factor Beta 1 (hTGF β 1) was purchased from R&D Systems (Minneapolis, MN). Mink Lung Epithelial Cells (MLEC) were obtained from American Type Culture Collection (MV 1 Lu ATCC No. CCL 64). T7 RNA polymerase, 2'-F-modified CTP and UTP were prepared in house. DNA oligonucleotides

were obtained from Operon Technologies, Inc. (Alameda, CA). All other reagents and chemicals were from commercial sources.

b) SELEX

The SELEX process has been described in detail in United States Patent No. 5,270,163 (see also Tuerk and Gold (1990) Science 249:505-510). The DNA templates contained either 40 (SEQ ID NO:1), 30 (SEQ ID NO:2) or 20 (SEQ ID NO:3) random nucleotides, flanked by 5' and 3' constant regions for primer annealing sites for PCR and cDNA synthesis (Table 1). The starting pool of single stranded DNA molecules were converted to double stranded DNA by primer extension reactions with the klenow fragment of DNA polymerase. RNA pools were prepared by transcription and were gel purified before use. Transcription reactions were done with about 5 μ M DNA template, 5 units/ μ L T7 RNA polymerase, 40 mM Tris-HCl (pH 8), 12 mM $MgCl_2$, 5 mM DTT, 1 mM spermidine, 0.002% Triton X-100, 4% PEG 8000, 2-4 mM each 2'-OH ATP, 2'-OH GTP, 2'-F CTP, 2'-F UTP, and 0.25 μ M α - ^{32}P -2'-OH ATP (800 Ci/mmol). At later rounds, RNA pools were prefiltered and/or preadsorbed with multiple layers of the same nitrocellulose filter type used in the SELEX process in order to reduce the frequency of molecules selected for nitrocellulose binding. To prepare binding reactions, the RNA molecules were incubated with recombinant hTGF β 1 in Dulbecco's Phosphate-Buffered Saline (DPBS) (Life Technologies, Gaithersburg, MD, Cat. No 21600-010) containing 0.01% human serum albumin and 1.0 mM $MgCl_2$. Following incubation at 37°C (10 minutes to 10 hours) the protein-RNA complexes were partitioned from unbound RNA by capture on nitrocellulose. Nitrocellulose filter bound RNA was recovered by phenol/urea extraction. The partitioned RNA was reverse transcribed into cDNA by AMV reverse transcriptase at 48°C for 60 minutes in 50 mM Tris-HCl pH 8.3, 60 mM NaCl, 6 mM $Mg(OAc)_2$, 10 mM DTT, 50 pmol DNA 3' primer 3G7 (SEQ ID NO:5; Table 1), 0.4 mM each of dATP, dCTP, dGTP, and dTTP, and 1 unit/ μ L AMV RT. The cDNA was PCR amplified and used to initiate the next SELEX cycle. PCR conditions were 2 μ M each 3G7 (SEQ ID NO:5) and 5G7 (SEQ ID NO:4) primers (Table 1), 50 mM KCl, 10 mM Tris-HCl, pH 9, 0.1% Triton X-100, 3 mM $MgCl_2$, 0.5 mM of each dATP, dCTP, dGTP, and dTTP, and 0.1 units/ μ L Taq DNA polymerase.

c) Nitrocellulose Filter Partitioning

To partition the protein-RNA complexes away from uncomplexed RNA, the binding reactions were filtered through nitrocellulose/cellulose acetate mixed matrix, 0.45 μ m pore size filter disks, type HA, (Millipore, Co., Bedford, MA). For filtration, the filters were placed onto a vacuum manifold and wetted by aspirating with 5 mL of DPBS. The binding reactions were aspirated through the filters, washed with 5 mL of DPBS + $MgCl_2$ and counted in a scintillation counter (Beckmann). At later rounds, nitrocellulose filters were preblocked with 2 mL of DPBS + 1 mM $MgCl_2$ + 0.01% BSA, and wash volumes were increased to 25 mL in order to reduce background binding to nitrocellulose. At later rounds in the SELEX process, 10 mL washes with 0.5 M urea were introduced to remove RNA that binds to nitrocellulose.

Nitrocellulose partitioning was also used for determining the equilibrium dissociation constants of RNA ligands to hTGF β 1. Binding curves obtained by nitrocellulose filtration indicated that RNA pools and some RNA ligands bind monophasically while others bind biphasically. Biphasic binding can be described as the binding of two affinity species derived from the same ligand sequence that can fold into alternate structures which are kinetically trapped and are not in equilibrium.

To obtain the equilibrium dissociation constants of RNA ligands to TGF β 1, the binding reaction:



where R=RNA, P=Protein and K_D =dissociation constant is converted into an equation for the fraction of RNA bound at equilibrium:

$$q = (f/2R_T)(P_T + R_T + K_D - ((P_T + R_T + K_D)^2 - 4P_TR_T)^{1/2})$$

where q=fraction of RNA bound, P_T =total protein concentration, R_T =total RNA concentration and f=retention efficiency of RNA-protein complexes. The average retention efficiency for RNA- hTGF β 1 complexes on nitrocellulose filters is 0.4-0.8.

Biphasic binding data were evaluated using the equation:

$$q = 2P_T + R_T + K_{D1} + K_{D2} - [(P_T + X_1R_T + K_{D1})^2 - 4P_TX_1R_T]^{1/2} - [(P_T + X_2R_T + K_{D2})^2 - 4P_TX_2R_T]^{1/2}$$

where X_1 and X_2 are the mole fractions of the affinity species R_1 and R_2 and K_{D1} and K_{D2} are the corresponding dissociation constants.

The K_D 's were determined by least square fitting of the data points using the software Kaleidagraph (Synergy Software, Reading, PA).

d) Cloning and Sequencing

RNA recovered from the filters of the final round of the SELEX process was reverse transcribed and PCR amplified as in previous rounds. The PCR products were purified by PAG electrophoresis and cloned into the SrfI restriction site of PCR-Script Direct SK(+) plasmid using the pCR-Script Amp SK(+) cloning kit (STRATAGENE CLONING SYSTEMS, La Jolla, CA). About 180 clones were sequenced with ABI Prism sequencing kit (Applied Biosystems, Perkin-Elmer, CT).

e) Analysis of nucleic acid ligand binding by BIAcore

Biotinylated TGF β 1 (catalog No. NFTG0, R&D Systems, Minneapolis, MN) was coupled onto an SA5 streptavidin BIAcore chip (BIAcore, Inc., Piscataway, NJ) by injecting biotinylated TGF β 1 solution as prepared per manufacturers instructions at 5 μ L/min to achieve loadings of 436, 133 and 57 response units (RU) in flow cells 1, 2 and 3, respectively. Flow cell 4 was kept blank for control and background subtractions. To measure binding activities, RNA ligands and antiserum (pan-specific anti-TGF β 1 total rabbit IgG, catalog No. AB-100-NA, R&D Systems, Minneapolis, MN) were injected at various concentrations in HBSMC-HSA (Hepes buffered saline pH 7.5, 1 mM MgCl₂, 1 mM CaCl₂, 0.01% human serum albumin) at 20 μ L/min. Injections allowed about 3 minute association and 3 minute dissociation cycles. Data were plotted and analyzed by BIAanalysis software (BIAcore, Inc., Piscataway, NJ).

f) Analysis of nucleic acid ligand specificity by BIAcore

Biotinylated 2'-fluoro-pyrimidine RNA nucleic acid ligands were transcribed in the presence of 5'-biotin-modified guanosine monophosphate (5'-biotin-GAP) as described in copending International Publication No. WO 98/30720, published July 6, 1998, the contents of which are incorporated herein by reference. Typical reactions were 1 mL in volume containing standard T7 RNA polymerase, 40 mM Tris-HCl (pH 8), 12 mM MgCl₂, 5mM DTT, 1 mM spermidine, 0.002% Triton X-100, 4% PEG 8000, with 3 mM each 2'-F-CTP and 2'-F-UTP, and 1 mM each ATP and GTP and 5 mM 5'-biotin GAP. Following overnight incubation at 37°C, transcripts were purified by gel electrophoresis and ethanol precipitation.

To prepare an analysis chip, three RNA species were used and were injected in HBSMC-HSA at 5 μ L/min. Flow-cells 1, 2 and 3 were loaded with 535, 536 and 563 RU of random 40N7 library, TGF β 1 ligand 40-03 (SEQ ID NO:84), and TGF β 1 ligand 40-60 (SEQ ID NO:128), respectively. Thus, for stoichiometric binding of RNA to TGF β 1 or TGF β 2, one would expect a maximum of approximately 500 RU's, since TGF β 1 and TGF β 2 have the same mass as the RNA. Flow cell 4 was kept blank for control and background subtractions. The analysis chip was exposed to various concentrations of TGF β 1 and TGF β 2 at 20 μ L/min. in HBSMC-HSA. Data were plotted and analyzed by Bialysis software (BIAcore, Inc., Piscataway, NJ).

g) *Inhibition of TGF β 1 mediated growth suppression of mink lung epithelial cells (MLEC)*

To determine the bioactivity of RNA pools and individual ligands, a growth assay was used in which TGF β 1 antagonists cause reversal of TGF β 1 growth suppression of mink lung epithelial cells. In this assay, MLEC were treated with various concentrations of random RNA, individual ligands, antibodies such as polyclonal anti-TGF β 1 antibody (pan-specific anti-TGF β 1 total rabbit IgG, catalog No. AB-100-NA, R&D Systems, Minneapolis, MN), monoclonal mouse anti-TGF β 2/TGF β 3 antibody (Genzyme Corp., Cambridge MA, catalog No. 1836-01) and monoclonal mouse anti-TGF β 1/ TGF β 2/ hTGF β 3 antibody (Genzyme Corp., Cambridge, MA, catalog No. 1835-01) in serum-free 48 hr-3T3-conditioned medium (CM).

Cells were plated at 10^5 /mL in 96-well plates in MEM, 10 mM HEPES and 0.2% FBS. Following 4 hours of incubation at 37°C, when cells appeared to attach to the well surface, TGF β 1 was added at 2 pM with or without TGF β 1 ligands that ranged from 0.1 nM to 1 μ M. In a second assay performed in order to determine cross-species reactivity, rather than using hTGF β , a conditioned serum-free medium (CM) was used. CM was conditioned by culturing it in murine 3T3 fibroblast for 48 hours. Before use, this conditioned medium was heat treated at 80°C for 10 minutes to activate the 3T3 cell derived TGF β and then it was diluted to 50% and supplemented with 0.2% murine serum. In each assay, hTGF β 1 (or CM) was diluted appropriately in MEM and FBS (0.2% or murine serum) and the ligands were diluted in MEM. TGF β 1 (or CM) and ligand dilutions at 10X the final concentration were premixed at equal volumes and then were added to the cells. Following addition of the TGF β 1 (or CM) -ligand mixture, the cells were incubated for 16-18 hours prior to addition

of ^3H -thymidine at 0.25 μCi per well and continued incubation for 7-8 additional hours. After incubation, the cells were washed and harvested with SKATRON filtering units and ^3H -thymidine incorporation in cellular DNA was quantitated by scintillation counting in Ecoscint. Data were plotted and analyzed as described in Park *et al.* (1990) J. Exp. Med. 171:1073) and Dower *et al.* (1984) J. Immunol. 132:751). K_i values were determined from inhibition IC_{50} values according to the equation $K_i = \text{IC}_{50} / (1 + ([T]/K_{dT}))$, where $[T]$ is the concentration in molar of TGF β 1 present in the assay and K_{dT} is the concentration of TGF β 1 causing 50% inhibition of MLEC proliferation as determined by TGF β 1 titration experiments.

Example 2. RNA ligands to hTGF β 1

a) TGF β 1 SELEX

Three parallel SELEX processes were performed with 2'-F pyrimidine modified RNA randomized at 40, 30 and 20 contiguous positions. The conditions for the SELEX process and results for each round are summarized in Table 2. The first round was done under two different conditions where RNA to protein ratios were 10:1 and 50:1. Each condition included a pool of 1.2×10^{15} (2000 pmoles) 2'-F pyrimidine modified RNA molecules. Resulting round 1 pools were mixed (at the transcription level) in equal portions for round 2. Random 2'-F pyrimidine modified RNA bound to hTGF β 1 with an approximate K_D of ~ 10 nM. The rounds of the SELEX process were continued until no further improvement in K_D was observed. Figures 1A and 1B show binding curves of rounds 0, 14, 15L and 16L of the 40N pool (Fig. 1A) and rounds 0, 14, 15 and 17 of the 30N pool (Fig. 1B). The 40N pools showed the best affinity improvement followed by the 30N pool. The 20N pool showed no significant improvement after 12 rounds of SELEX. The RNA pools from the final rounds (round 16, 17 and 12 for the 40N, 30N and 20N, respectively) were reverse transcribed, PCR amplified and cloned as previously described (Pagratis *et al.* (1997) Nature Biotechnology 15:68-73). The 20N pool was cloned and sequenced as a control.

b) RNA sequences

The sequences of 64, 48, and 40 clones from the 40N, 30N and 20N final evolved pools, respectively, were determined and are summarized in Table 3 (SEQ ID NOS:6-143) in standard single letter code (Cornish-Bowden (1985) Nucleic Acid Res. 13:3021-3030).

Ligand designations in Table 3 include the size of the contributing random region followed by the ligand ID number. Ligands appearing more than once are designated with multiple ID numbers corresponding to their frequency. Ligands differing by one base are considered PCR derived variants of the same original molecule. Computer assisted global and local alignments suggest alignments and family assignments as shown in Table 4. There are 9 proposed families of which the first three include only 40N ligands. The remaining families contain clones derived from all three pools. However, it is clear from sequence lengths that cross contamination of the three pools had occurred. The possibility of cross contamination was minimized by electrophoretic size fractionation of RNA at each round, and PCR products prior to cloning.

Example 3. Binding Affinities of hTGF β 1 Ligands

The dissociation constants of the hTGF β 1 ligands were determined by nitrocellulose filter binding and are listed in Table 4. The majority of ligands bind hTGF β 1 biphasically. Under conditions of protein excess, biphasic binding suggests that ligands can exist as two affinity species (presumably isoconformers) that are not in equilibrium, i.e. isoconformers that are kinetically trapped. The best identified ligands, 40-03 (SEQ ID NO:84) and 40-60 (SEQ ID NO:128) bind biphasically with the high and low affinity dissociation constant of ligand 40-03 at about 0.3 pM and 4.6 nM, respectively. There are observed variabilities in the K_D determinations for individual clones and random RNA, however, the high affinity species of ligands 40-03 and 40-60 always show about $>10^4$ better affinity than random RNA in any given experiment. A significant difference between random RNA and ligands 40-03 and 40-60 was also observed by BIAcore analysis. In the BIAcore analysis, biotinylated TGF β 1 was coupled to a BIAcore chip and exposed to various concentrations of random RNA, ligand 40-03 and ligand 40-60. Also in this experiment the binding activities of ligands 40-03 and 40-60 were compared with the binding activity of an anti-TGF β 1 polyclonal antibody (catalog No. AB-100-NA, R&D Systems, Minneapolis, MN). Figure 2 shows the ligand binding of the random RNA, ligands 40-03 and 40-60, and of the anti-TGF β 1 antibody. From these Biacore data the determined dissociation rate constant (k_{off}) for ligand 40-03, ligand 40-60 and anti-TGF β 1 were about 2.7×10^{-4} , 7.0×10^{-4} and 4.4×10^{-5} , respectively. Therefore, ligands 40-03 and 40-60 show binding properties similar to the

control antibody with the off rate of 40-03 being about 6 fold faster than the off rate of the anti-TGFB1.

Example 4. Specificity of RNA Ligands to hTGFB1

The specificity of ligands 40-03 (SEQ ID NO:84) and 40-60 (SEQ ID NO:128) to TGFB1 was tested by comparing their dissociation constants with the closely related protein TGFB2 and the heparin binding human growth factors hVEGF and hKGF. The results summarized in Table 5 show that ligands 40-03 and 40-60 are specific for hTGFB1. Ligands 40-03 and 40-60 have binding affinities similar to random RNA to the other proteins tested.

These ligands are four to five orders of magnitude more specific for TGFB1 than even closely related proteins such as TGFB2 and other heparin binding growth factors. Of particular interest is the ability of these TGFB1 ligands to discriminate between TGFB1 and TGFB2 since these two proteins share 72% identity and are interchangeable in most biological assays (Roberts and Sporn (1991), "The Transforming Growth Factor- β 's" in Peptide Growth Factors and Their Receptors, M. B. Sporn and A. B. Roberts, eds. (New York: Springer-Verlag)). Recently the solution three-dimensional structure of TGFB1 has been described and compared to the X-ray structure of TGFB2 (Hinck *et al.* (1996) *Biochemistry* 35:8517-8534). Based on this comparison there is only a slight structural difference between TGFB1 and TGFB2 with a maximum root mean square deviation of 1.9 Å (Hinck *et al.* (1996) *Biochemistry* 35:8517-8534). BIAcore technology was also utilized to compare the binding specificity of ligands 40-03 and 40-60 between TGFB1 and TGFB2. The analysis chip, loaded with either biotinylated 40-03, biotinylated 40-60, or biotinylated random RNA was exposed to various concentrations of TGFB1 or TGFB2 at 20 μ L/min in HBSMC-HSA, and data was collected during the association phase (3 min) and the dissociation phase (3 min).

Figures 3A-3F show a typical nested series of sensorgrams with TGFB1 and TGFB2 binding to random RNA, ligand 40-03 and ligand 40-60. These BIAcore results show that when applied at high concentrations, TGFB1 binds random RNA (Fig. 3A), ligand 40-03 (Fig. 3B) and ligand 40-60 (Fig. 3C) equivalently in a nonspecific manner with fast on-rates and off-rates. This non-specific binding is low affinity and non-stoichiometric, since stoichiometric binding would result in about 500 RU's of TGFB1 bound to the RNA on the chip (see Example 1(f)). This non-specific binding represents the binding of random RNA

to TGF β 1 also observed by nitrocellulose filter binding (see Example 2(a)). When applied at lower concentrations, (less than 50 nM) TGF β 1 binds ligand 40-03 and 40-60 but not random RNA. The specificity of TGF β 1 for ligands 40-03 and 40-60 is mainly due to slower off rates compared to random RNA. This represents a specific interaction which appears to be stoichiometric, since the binding curves at this concentration plateau at about 400 RU's and the dissociation rates are very slow. See, for example, the triangles in Figure 3B, in which the dissociation rate is almost flat.

TGF β 2 behaves differently in the same experiment. TGF β 2 shows no binding to random RNA (Fig. 3D) and some binding to ligand 40-03 (Fig. 3E) and ligand 40-60 (Fig. 3F). This difference in binding affinity to random RNA is consistent with the increased negative charge content of TGF β 2 compared to TGF β 1. The results in Figures 3D-3F clearly show that TGF β 2 binds ligands 40-03 and 40-60 better than random RNA. However, the observed TGF β 2 binding to ligand 40-03 and 40-60 is still different, and lower than the corresponding binding of TGF β 1. It seems that TGF β 2 binds ligand 40-03 and 40-60 with a very slow on and off rate suggesting induced fit. These results suggest that ligands 40-03 and 40-60 show cross-reactivity and bind to both TGF β 1 and TGF β 2 but with different affinities and kinetics.

Example 5. Inhibition of TGF β 1 bioactivity

TGF β 1 is a multifunctional growth factor (Roberts and Sporn (1991), "The Transforming Growth Factor- β 's" in Peptide Growth Factors and Their Receptors, M. B. Sporn and A. B. Roberts, eds. (New York: Springer-Verlag)). One of its activities is inhibition of proliferation of epithelial cells. For example, TGF β 1 causes mink lung epithelial cells (MLEC) to cease replication, and it is manifested by reduction in 3 H-thymidine incorporation. The midpoint of this response of MLEC is about 0.3 pM.

RNA from round 11 and 14 of the 40N and 30N pools along with random RNA controls were tested for TGF β 1 inhibitory activity using mink lung epithelial cells and measuring 3 H-thymidine incorporation in the presence of 2 pM hTGF β 1. A significant hTGF β 1 inhibitory activity was observed with these advanced pools and not with random RNA (Figures 4A and 4B). It appears that the 40N round 14 pool was neutralizing serum-derived TGF β 1 in addition to the supplied TGF β 1 since the amount of DNA synthesis at

high RNA concentrations is greater than that observed without exogenously added TGF β 1 (Fig. 4A).

Using the same MLEC assay several individual ligands were screened for TGF β 1 inhibitory activity. The results are summarized in Table 4 (Ki column). Several ligands were found that are good inhibitors of hTGF β 1. Typical results are shown in Figures 5A-5D. It seems that the majority of good inhibitors belong in class 1 which contains only ligands from the 40N (Table 4, Ki column), and as expected, the best bioactivity correlated with binding activity.

TGF β 1 proteins of various species are highly conserved proteins. The human and mouse or rat TGF β 1 differ by a single amino acid. To determine the cross-species specificity, the ability of the TGF β 1 ligands to inhibit the murine (m)TGF β 1 bioactivity was tested. Since mTGF β 1 is not commercially available, conditioned media from mouse cells was used. Several cell lines were screened for TGF β 1 activity and it was found that 3T3 cells were the best source. Figure 6 shows the specificity of conditioned media used and the ability of ligand 40-03 and 40-60 to inhibit the bioactivity of such conditioned media. Inhibition profiles with a pan-specific antibody (monoclonal mouse anti-TGF β 1/TGF β 2/TGF β 3 antibody; Fig. 6, open triangles) and a TGF β 2/TGF β 3 specific antibody (Fig. 6, open circles) demonstrate that the ability of the 3T3 conditioned media to inhibit the growth of MLEC is mainly due to TGF β 1. Figure 6 also clearly demonstrates that, as expected, ligands 40-03 and 40-60 can inhibit the bioactivity of the 3T3 CM, presumably due to mTGF β 1.

Example 6. Effect of library random region length on the outcome of the SELEX

The above results suggest that size of the random region is important for the outcome of the SELEX process with TGF β 1 in terms of obtaining bioactive ligands. These data are summarized in Table 6. It appears that the 30N pool contained ligands that bind TGF β 1 with good affinities but these 30N ligands in general fail to inhibit the TGF β 1 bioactivity. The 20N pool failed to yield any TGF β 1 ligands. Only the 40N pool yielded ligands that bind TGF β 1 and inhibit its bioactivity.

Example 7. Proposed secondary structure of bioactive TGF β 1 Ligands

5 The predicted common secondary structures among those ligands that could inhibit TGF β 1 bioactivity were investigated. These ligands appear to accommodate the proposed structure shown in Figure 7 which is a double pseudoknot. This structure is consistent with enzymatic digestion results obtained with three bioactive class 1 ligands. Such enzymatic digestion confirmed stem 1 and stem 2 while stem 3 was postulated on the basis of truncation results.

TABLE 1Starting ssDNA templates

40N7:

5'GGGAGGACGATGCGG[-40N-]CAGACGACTCGCCCCGA 3'

SEQ ID NO: 1

30N7:

5'GGGAGGACGATGCGG[-30N-]CAGACGACTCGCCCCGA 3'

SEQ ID NO: 2

20N7:

5'GGGAGGACGATGCGG[-20N-]CAGACGACTCGCCCCGA 3'

SEQ ID NO: 3

SELEX PCR Primers:

5G7:

5'TAATACGACTCACTATAGGGAGGACGATGCGG 3'

SEQ ID NO: 4

3G7:

5'TCGGGCGAGTCGTCTG 3'

SEQ ID NO: 5

TABLE 2. TGF β 1 SELEX conditions and results

<u>Round</u>	<u>[P]¹, nM</u>	<u>[R]², nM</u>	<u>%B³</u>	<u>S/N⁴</u>	<u>PF⁵</u>	<u>PB⁶</u>	<u>Spin⁷</u>	<u>Bf. Wash⁸</u>	<u>U. Wash⁹</u>
<u>40N</u>									
1A	100	5000	0.42	13	-	-	-	5	
1B	100	1000	0.60	30.7	-	-	-	5	
2	100	500	0.98	4.9	+	-	-	5	
3	100	500	3.40	2.6	+	-	-	10	
4	100	500	4.90	2.9	+	-	-	10	
5	33	167	2.50	1.9	+	-	+	10	5
6	33	167	ND	ND	+	-	+	10	55
7	11	56	1.00	8.0	+	+	+	10	55
8	11	56	0.40	5.0	+	+	+	10	55
9	3.3	16.5	ND	13.7	+	+	+	10	55
10	1.1	5.6	1.55	16.5	+	+	+	5	5
11	0.33	1.5	2.00	7.0	+	+	+	5	5
12*	0.03	0.15	1.31	8.0	+	+	+	5	5
13*	0.0033	0.016	0.33	2.4	+	+	+	5	5
14*	0.011	0.055	1.00	3.5	+	+	+	5	5
15L	0.033	0.0066	10.00	130.0	+	+	+	5	5
16L	0.033	0.0066	11.50	345	+	+	+	5	5
<u>30N</u>									
1A	140	7000	0.36	4.4	-	-	-	5	
1B	140	1400	1.80	20.9	-	-	-	5	
2	140	700	1.90	11.1	+	-	-	5	
3	140	700	4.60	4.4	+	-	-	10	
4	140	700	5.20	9.0	+	-	-	10	
5	5.0	25.6	1.50	4.3	+	-	+	10	5
6	11	55	0.70	2.6	+	-	+	10	55
7	3.3	16.5	0.26	1.7	+	+	+	10	55
8	3.3	16.5	0.10	2.0	+	+	+	10	55
9	3.3	16.5	ND	14.4	+	+	+	10	55
10	1.1	5.6	0.39	4.5	+	+	+	5	5
11	0.33	1.5	0.38	4.0	+	+	+	5	5
12*	0.03	.15	0.40	3.0	+	+	+	5	5
13*	0.03	.16	0.49	3.0	+	+	+	5	5
14	0.11	.55	0.90	10.0	+	+	+	5	5
15	0.033	0.165	0.50	6.7	+	+	+	5	5
16L	0.11	.022	1.8	25.7	+	+	+	5	5
17L	0.033	0.0066	1.5	13.6	+	+	+	5	5

Table 2 continued:

<u>Round</u>	<u>[P]¹, nM</u>	<u>[R]², nM</u>	<u>%B³</u>	<u>S/N⁴</u>	<u>PF⁵</u>	<u>PB⁶</u>	<u>Spin⁷</u>	<u>Bf. Wash⁸</u>	<u>U. Wash⁹</u>
20N									
1A	1000	50000	0.54	15.8	-	-	-	5	
1B	100	1000	1.70	39.5	-	-	-	5	
1C	1000	5000	3.80	51.0	-	-	-	5	
2	1000	5000	3.70	72.5	+	-	-	5	
3	1000	5000	5.90	122.0	+	-	-	10	
4	330	1670	1.70	17.4	+	-	-	10	
5	4.0	20.6	1.00	10.6	+	-	+	10	5
6	1.2	6.1	0.60	4.7	+	-	+	10	10
7	3.3	16.5	0.06	3.0	+	+	+	10	55
8	3.3	16.5	0.30	15	+	+	+	10	55
9	3.3	16.5	ND	6.6	+	+	+	10	55
10	3.3	16.5	0.31	16.5	+	+	+	5	5
11	1.1	5.6	0.19	4.0	+	+	+	5	5
12	1.1	5.6	1.2	13.0	+	+	+	5	5
13L	0.1	0.022	0.9	10.0	+	+	+	5	5

¹Protein concentration in nanomolar²RNA concentration in nanomolar³Background expressed as % of input⁴Signal to noise⁵Use of nitrocellulose prefiltered RNA⁶Use of preblocked nitrocellulose with BSA⁷Spinning of binding reactions before filtering through nitrocellulose⁸Volume in ml of buffer wash⁹Volume in ml of 0.5M urea wash¹⁰L indicates RNA limiting SELEX conditions¹¹The RNA pool used was a mixture of 2-3 pools obtained from 3 fold serial dilutions of a binding reaction. Only the most stringent condition is shown.

TABLE 3. Sequence of individual TGFβ1 RNA ligands. The sequences of the fixed regions (Table 1) are not shown.

	SEQ ID NO:
20-01	GUCUAUUUUUGCCUCCUCCC
20-02	AAUCCUUUCUUAACCCUCCC
20-03	UGUCUUUAGCUUAGGUUAUCCUUCUGCCG
20-04	UGUCUUUAGCUUAGGUUAUCCUUCUGCCG
20-05	UGUCUCUACCUUAGGUUAUCCUUCUACCG
20-06	UGAGUCUUGUUUUUUCGUC
20-07	UUGGCAUUGAAAGAGCUGGCAUACAUUGGC
20-08	UCCUUUCUAAAUUCCUCCC
20-09	GUCGUUGUUUUUCUCCUCCC
20-10	UGAGUCUUUCUUUUCGUCCC
20-11	GUCGUUUUUUGGUCCUC
20-12	GUUUUAUUAUUCGUUUGGC
20-14	GUCGAUCAUUUUUAGCCUCCC
20-17	UGAGUUGAUCUUUUCGUCCC
20-18	UGCCUUUAGCUUAGGCAUUGCCUUCUGUG
20-19	CAAAUUUUUGGUCAAGCCGUAUUUGCCGC
20-21	GUCGUUCUUUUUCCUCCC
20-23	AAUUUUUGUGAAGACGUUUGCCGCUUUGCC
20-24	CGCAUCUCUGUUUUUCUCCC
20-25	GGAUUUUUUGGUAAAGCCGUUAGCCUCCG
20-26	UCAUCUCUGGGAGUUAAGAUAUUUGGCCG
20-27	GCAGCCUCUGAUUUUUCUCCC
20-28	GUCGUAUUUUUGGUUCUGCC
20-29	GUCGUAUUUUUCCGCCUCCC
20-31	UCCUCAGCCUCUCACUAUAUCCUCCC
20-34	GUCUACUUGUUUACCUCCC
20-35	CGAUUUUUUCGUUUUUGGC
20-36	UGUCUAUAGCCUUGAUUAUAUCAUCUGCCG
20-37	CGAUUCCUUCUUUACUCCC
20-38	UCCCAUUUUUCUCCUCCC
20-40	GUUAAUUUUUUGUCCUCCG
20-41	UUUUUUUCUUUUUUCUUUUUUUCCG

Table 3 cont'd

	SEQ ID NO:
20-42	38
20-43	39
20-45	40
20-46	41
20-47	42
20-48	43
20-49	44
20-50	45
30-01,07,18,23	46
30-02	47
30-03	48
30-04	49
30-05	50
30-06	51
30-08	52
30-09,42	53
30-10	54
30-12,24,21,40,41	55
30-15	56
30-16,27,38,46	57
30-17	58
30-19	59
30-20	60
30-22	61
30-25	62
30-26	63
30-28	64
30-29	65
30-30	66
30-31	67
30-32	68
30-33	69
30-34	70
30-35	71

UCGUCUUUUGUUUUUCUCCC	
UGUCUAUAGCCUUGAUACAUCUUGCCG	
UGCCUUUAGCUUAGGCAUUGCCUUCUGCCG	
UGUCUAUAGCUUUGAUUUUAAUUUUCUGCCG	
UUUAUUUUUCUGUCUGGC	
GAUGAACCGAACCGAGGUUAGGUGCCAGAGAGCGCUCAU	
UGUCUAUUUUUUCCUCCC	
CUUUCGUCUGUUUUUCUGCC	
UGUCUUUAGCCUAGGUAUCCUUCUGCCG	
CCUUGUUUUUUUUUUUUUUCACCCC	
UGUCUUUAGCCAGGUGAUUCCUUCUGCCG	
UUAACCGUAAAGACGGCAUGAUAGUCCG	
UUUUUUUAGCUUAGGUAUUGCUUCNCCU	
UGCCUUUAGCUUAGGCUUUGCCUUCUGCCG	
CGAAUUUUUGUUGAGCCGUAUGCCG	
UGCCUUUAGCUUAGGUAUCCUUCUGCCG	
UGUCUUUAGCCUAGGUAUCCUUCUGCCG	
30-12,24,21,40,41UGUCUAUAGCCUGAUUUUUAAUCUGCCG	
UUGACCGUUAAGACGGCAUGUGGUCG	
UGCCUUUAGCUUAGGCAUUGCCUUCUGCCG	
UGCCUUUAGCUUAGGCUUUGCCUUCUGCCG	
UUAACCNAAUACGGCUUGANUUCUUCG	
UGCCUUUAGCUUAGGCAUUGCCUUCUGCCG	
UUAACCGUAAAGACGGCAUGAUUUUUCG	
UUGGCAUUGAAAGAGGCGUCAUAGUUCGC	
CCUUUCUUUUUUUUUUUUUCCUCCC	
UGCCUUUAGCCUAGACCUUGUCUUUCUGCCG	
UGUCUUUAGCCUAGGUAUCCUUCUGCCG	
UGUCUUUAGCCUAGGUAUCCUUCUGCCG	
ACCGGUAAGGCGACUGCAGGAACAAUCCCUAUGCGAC	
GGAAUUUUUGGUAAGCCGUAUGCCUCG	
UGGCAUUUGAAAGAGUCCGAUACCUUCG	
UGUCUAUAGCCUUGAUUACAUCUUGCCU	
UGUCUUUAGCCUAGGUAUCCUUCUGCCU	

Table 3 cont'd

[illegible]

Table 3 cont'd

40-72	UUAGGGGGUGUCAAACACCGCUAUUACAACUUUUCGCUUCCC	SEQ ID NO:
40-73	CUUCUUUUUCUUCUUUUUUUUUAUGUCUUCUUAUGCCG	139
40-75	GACCNUGUNUGCGAUUCAAACUCGUAAGGUCUUCUCACGUG	140
40-77	UUUAGGGGGUGUCAAACACCGCUAUUACAACUUUUCGCCCC	141
40-79	UUUAGGGGGUGUCAAACACCGCUAUUACAACUUUUCGCCCC	142
		143

Class 1

		<u>KdI (nM)</u>	<u>Kd2 (pM)</u>	<u>P1(%)</u>	<u>P2(%)</u>	<u>P2/P1(%)</u>	<u>Ki nM</u>
40-03	GGGUUA	UUGGGCGUCAACAUCGCCGGAU	UCUUUUUA	CGUC	4.6±1.1	0.3±0.08	0.4
40-06	UUA	GGGGCGUCAACACCCGCU	AU CAUAAUUUU	CGCCUUC	3.7±0.6	1.6±0.6	40.5
40-14	CAUUA	UGGGCGUCAACAU GCCGUUUCGAUUCUAUUGC			5.7±1.4	0.4±0.2	16.7
40-16	UUA	GGGGCGUCAACACCCGCU	AU UACA UCUUU	CGCCUUC	1.7±0.6	0.06±0.04	3.9
40-19	UUA	GGGGCGAGUUCAACACCCGCU	AU GUGAUUCUUU	CGCCUUC	4.2±2.2	3.7±2.7	0.6
40-22, 35	UUA	GGGGCGUCAACACCCGCU	AU UACAAUUUU	CGCUUCC	13.9±4.3	17.6±4.5	28.0
40-23	UUA	GGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCUUCC	14.2±4.5	15.6±4.0	
40-24	UUA	UGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCUUUC	12.7±4.7	27.5±10.2	0.75
40-26	UUA	GGGGCGUCAACAUUCGCU	AU UACAAUCUU	CGCCUUC	7.7±1.6	40.8±23.3	
40-28	UUA	GGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCCUAC	12.3±2.4	81.6±47.2	
40-31	UUA	AGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCUUCC	8.4±2.8	0.7±0.4	
40-32	UUA	UGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCCUC	14.0±6.4	5.0±3.3	2.56
40-42	UAGCGCGAGUUCAACACCCGCU	AU GUGACUCUUU	CGCCUCC	11.4±1.9	0.09	6.2	38
40-54	UUA	GGGGCGUCAACACCCGCU	AU CAUAAUCUU	CGCUUCC	8.5±1.8	6.75±9	
40-55	UUA	GGGGCGUCAACACCCGCU	AU U CAACUU	CGCUUCC	8.0±2.5	0.1±0.06	2.9
40-56	UUA	GGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCCUCC	4.2±1.3	0.2	7.4
40-58	UUA	UGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCCUCC	4.4±1.6	5.3±2.2	0.9
40-60	UUA	UGGGCGUCAACACCCGCU	AU UACAGUUUU	CGCCUCC	3.8±1.5	1.9±0.8	0.8
40-61, 76	UUA	GGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCUUCC	13.5±4.2	1.0±0.8	
40-64	UUA	GGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCUUCC	5.6±2.0	3.1±1.8	
40-68	UUA	GGGGCUCAACACCCGCU	AU UACAUUCUU	CGCCUCC	20.7±3.2	0.4±0.3	41.3
40-72	UUA	GGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCUUCC	1.4±0.8	0.07±0.05	3.0
40-77	UUA	UGGGCGUCAACACCCGCU	AU UACAAUCUU	CGCCCC	3.7±1.5	1.73±1.43	?
40-79	UUA	UGGGUGUCAACACCCGCU	AU UACAAUCUU	CGCCUCC	0.6±0.1	0.5±0.4	60.4
							12.23
							66

Class 2

39

40-66	UUCAAGGUUACGCCUGCGGACCCUGCGCCAAACAUCUCCC
40-67	CUCAAGGUUACGCCUGCGGACCCUGCGCCAAACAUCUCCC
40-69	CACAAAGUUACGCCUGAGGACCCUGCGCCAAACAUCUCCC

KdI (nM)	P1 (%)	P2 (%)	P2/P1 (%)	K _i , nM
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Class	Sequence	Kd1 (nM)	Kd2 (pM)	P1 (%)	P2 (%)	P2/P1 (%)	Ki, nM
40-12	GACCCUUGUCUGCGGAUCAAACUCGUAGGUUUUCUACGUG	5.5±0.7	0.7±0.2	64.7	10.0	15.5	6.88
40-21, 34	GACCCUUGUCUGCGGAUCAAACUCGUAGGUUUUCUACGUG	10.1±3.5	6.5±4.0	100	9.3	9.3	1.68
40-29	GACCCUUUUUCUGCGGAUCAAACUCGUACGUUUUCUACGUG	10.9±5.5		100			>1300
40-53	GACUCUUGUCUGCGGAUCAAACUCGUAGGUUUUCUACGUG						2.25
40-75	GACCCUUUGUNUGCGGAUCAAACUCGUAGGUUUUCUACGUG						

Table 4 cont'd
Class 4

		<u>Kd1 (nM)</u>	<u>Kd2 (pM)</u>	<u>P1 (%)</u>	<u>P2 (%)</u>	<u>P2/P1 (%)</u>	<u>Ki. nM</u>
20-03	UGUCUUUAGCUUAGG						
20-04	UGUCUUUAGCUUAGG	0.11±0.1	0.3±1.7	9.3	13.4		
20-05	UGUCUCUACCUUAGG	0.2		8.0			
20-18	UGCCUUUAGCUUAGG	0.11±0.1		10.49			
20-36	UGUCUAUAGCCUUGA						
20-43	UGUCUAUAGCCUUGA						
20-45	UGCCUUUAGCCUUGA						
20-46	UGUCUAUAGCCUUGA						
30-01, 07, 18, 23	UGUCUUUAGCCUAGG	3.4		63			
30-03	UGUCUUUAGCCUAGG						
30-05	UUUUUUUAGCUUAGG	58.2	262	~100	1.2		
30-06	UGCCUUUAGCUUAGG	100					
30-09, 42	UGCCUUUAGCUUAGG	56.5	74.1	~100	2.4		
30-10	UGCCUUUAGCUUAGG	5.35±0.9		22.7			
30-12, 24, 21, 40, 41	UGUCUUUAGCCUAGG	4.05±1.5	75.5	28.6	17.9	62.6	40
30-14	UGUCUAUAGCCUAGG	2.82±1.7	60.8	24.8	23.2	93.5	>300
30-16, 27, 38, 46	UGCCUUUAGCUUAGG						
30-17	UGCCUUUAGCUUAGG	71.8	211±90	99.8	4.3	~4	
30-20	UGCCUUUAGCUUAGG	67					
30-28	UGCCUUUAGCCUAGA	2.57±0.3	205±93	99.9	4.3	~4	
30-29	UGUCUUUAGCCUAGG	0.78±0.07	0.7	22.9	6.1	26.6	
30-30	UGUCUUUAGCCUAGG		0.4±0.2	17.9	8.4	46.9	>130
30-34	UGUCUAUAGCCUUGA						
30-35	UGUCUAUAGCCUUGA	9.5±1.6		68.5			
30-36	UGCCUUUAGCUUAGG	20.7±13.8	224±123	90.3	8.8	9.7	
30-37	UGUCUUUAGCCUAGG	3.9±1.1		46.6			
30-39	UGUCUUUAGCCUAGG	2.65±0.7		46.6			
30-43	UGUCUUUAGCCUAGG	6.02±1.5	32.5±16.2	48.5	13.3	27.4	
	UGUCUUUAGCCUAGG	50.5		100			

Table 4 cont'd

		<u>Kd1 (nM)</u>	<u>Kd2 (pM)</u>	<u>P1 (%)</u>	<u>P2 (%)</u>	<u>P2/P1 (%)</u>	<u>Ki, nM</u>
30-44	UGCCUUUAGCUUAGG						
40-04	AUGCCUUUUGCCUUCAGGGUGU CAUUGC CUUGCCG	5.0±0.6	1.4±1.2	56.7	4.2	7.4	
40-11	UGCCUUUAGUC UGAUUCUUCUACCA UGAUUC UCUGCCG	4.6±0.7	4.9±3.1	68.9	8.0	11.6	
40-39	UGCCUUUAGCC UAAUUG AUCUAUUCAGCUU UCUGCCG	11.5±2.0	8.78±6.4	64.2	3.6	5.6	
40-41	UGCCUUUAGCC UGAGU AU ACUGAUGUAUUAUC UCUGCCG	3.8±0.9	1.4±1.1	30.8	11.1	36.0	>130
40-51	UGCCUUUAGUC UGAAUCUU ACCAUGCGAUUU UCUGCCG						
Class 5							
20-26	UCAUCUCUGGGAGUUUAAGAUCAUUUUGCCG						
30-04	UUAACCGUAAAGACGGCAUGAUGUAGUCCG	5.03±0.8		33.2			
30-15	UUGACCGUUAAGACGGCAUGAUGUGGUCCG	55.3		95.1			
30-19	UUAACCNUAAAUACGGCUUGANUUCUUCGG	5.7±1.9	346	28.8	13.6	47.2	53-52
30-22	UUAACCGUAAAGACGGCAUGAUGUUUUCGG	2.47		32.2			41
30-47	UUAACCGUAAAGACAGCAUGAUGUAGUCUG						
30-49	UUAACCGUAAAGACGGCAUGAUGUUGUCCG						
Class 6							
20-19	CAAAUUUUUUGGUCAAGCCGCUCAUUUGCCG						
20-23	AA UUUUUGUGAAGACGUU UGCCGCUUUGCC						
20-25	GGAAUUUUUGGUAAAGCCG UA UGCCUCGC						
30-08	CGGAUUUUU GUUGAGCCG UA UGCCGC	10.2±2.9		33.8			
30-32	GGAAUUUUUUGGUAAAGCCG UA UGCCUCGC						
30-50	GGAAUUUUUUGGUAAAGCCG UA UGCCUCGC						
Class 7							
20-07	UUGGCAUUGAAAGAGCUGGCAUACAUAUCCG						
30-25	UUGGCAUUGAAAGAGGCGUCAUAUGUUCGC	23±6.4	1.14±.6	79	2.7	3.4	
30-33	UUGCAUUGAAAGAGAUCCGCAUAUCCUUCGC						

Table 4 cont'd

Class 8

	<u>Kd1 (nM)</u>	<u>Kd2 (pM)</u>	<u>P1 (%)</u>	<u>P2 (%)</u>	<u>P2/P1 (%)</u>	<u>Ki, nM</u>
20-48						
30-31	100					
40-38	21.8±5.3					
			92.7			

Class 9

	<u>Kd1 (nM)</u>	<u>Kd2 (pM)</u>	<u>P1 (%)</u>	<u>P2 (%)</u>	<u>P2/P1 (%)</u>	<u>BCG (%)</u>	<u>Ki, nM</u>
20-01							
20-02							
20-06	0.6		5			0.6	
20-08	0.3		5			0.5	
20-09							
20-10							
20-11							
20-12							
20-14							
20-17							
20-21							
20-24							
20-27							
20-28							
20-29							
20-31							
20-34							
20-35							
20-37							
20-38							
20-40							
20-41							
20-42							
20-47							

[illegible]

Table 4 continued

Kd1 = Dissociation rate constant in nanomolar of the low affinity component of biphasic binding curves or dissociation rate constant in nanomolar of monophasic binding curves
Kd2 = Dissociation rate constant in picomolar of the high affinity component of biphasic binding curves
P1 = Plateau values in % of monophasic curves or of the low affinity component of biphasic curves
P2 = Plateau values in % of the high affinity component of biphasic curves
P2/P1 = Fraction in % of the high affinity component of biphasic curves
Ki = Inhibition constant in nanomolar obtained from the MLEC assay
BCG = Nitrocellulose binding background expressed as % of input

TABLE 5. Binding Specificity of TGF β 1 Ligands 40-03 and 40-60

Target	$K_D^{\text{Target}} / K_D^{\text{hTGF}\beta 1}$ 40-03	$K_D^{\text{Target}} / K_D^{\text{hTGF}\beta 1}$ 40-60
hTGF β 1	1	1
hTGF β 2	>340,000	>340,000
hKGF	>34,000	>34,000
hVEGF	>340,000	>340,000

When applicable, the high affinity component of biphasic binding was used.

TABLE 6. Results of TGF β 1 SELEX with random regions of 20 30 and 40N expressed by the distribution of ligands in the different classes and the binding and inhibitory activity of these classes

	SELEX Pools		Affinities		
	40N	30N	20N	Biph ¹ .	K _D -pM ² K _i ³
Total clones	64	48	40		
Unique clones	61	37	40		
Class 1	39.3%			+	+++
Class 2	26.2%			-	-
Class 3	8.2%			+	++
Class 4	8.2%	56.7%	20.0% ⁴	+	±
Class 5		16.2%	2.5% ⁴	+	+
Class 6		8.1%	7.5% ⁴	-	ND
Class 7		5.4%	2.5% ⁴	±	ND
Class 8	1.6%	2.7%	2.5% ⁴	-	ND
Class 9	16.4%	10.8%	65.0%	NC ⁵	-
Length of 40	59 (96.7%)	1 (2.7%)		1 (2.5%)	
Length of 30	1 (1.6%)	36 (97.3%)		15 (37.5%)	
Length of 20	1 (1.6%)		24 (60.0%)		

¹Biphasic binding is shown by plus (+), monophasic by minus (-), and unclear results by plus/minus (±)

²Low pmolar K_D values are shown by plus (+) and K_D values similar to random RNA are shown by minus (-)

³High, intermediate, low, and possible bioactivity is shown by 3 pluses (+++), two pluses (++)
one plus (+) or plus/minus (±), respectively

⁴longer than 20N

⁵nitrocellulose binders

WE CLAIM:

1. A purified and isolated non-naturally occurring RNA ligand to TGF β 1 wherein said ligand is selected from the group consisting of the sequences set forth in Table 3 (SEQ ID NOS: 6-143).

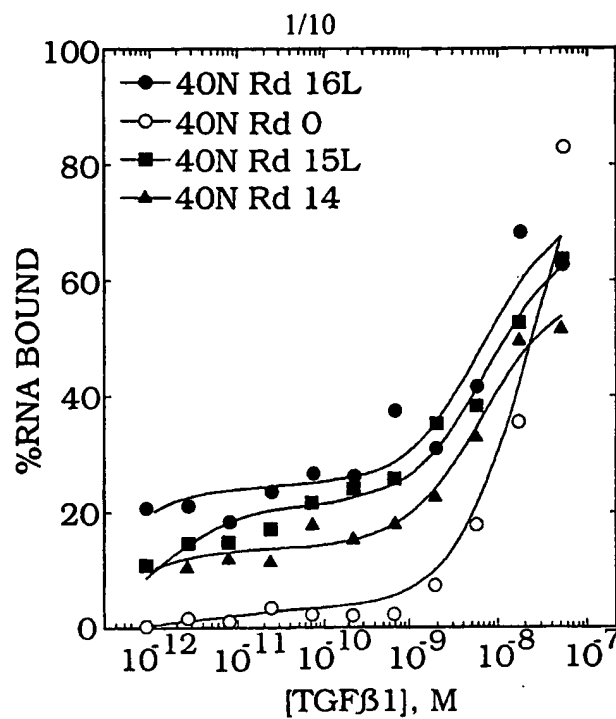


Figure 1A

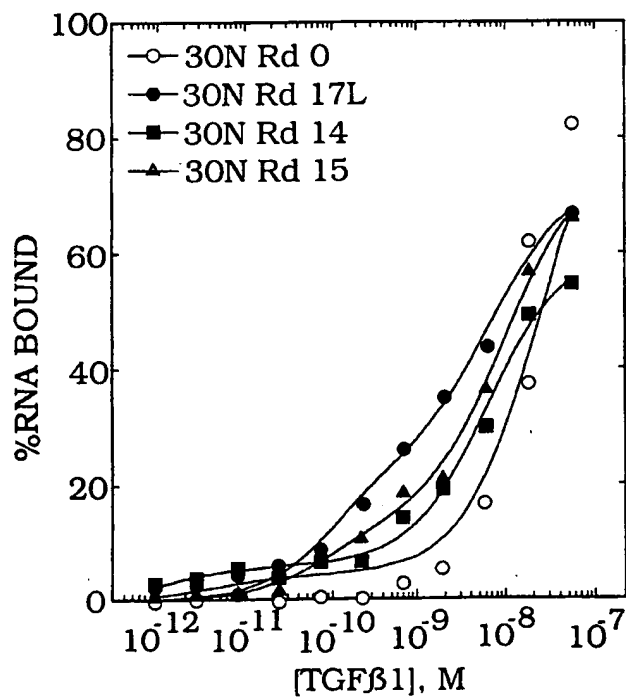


Figure 1B

2/10

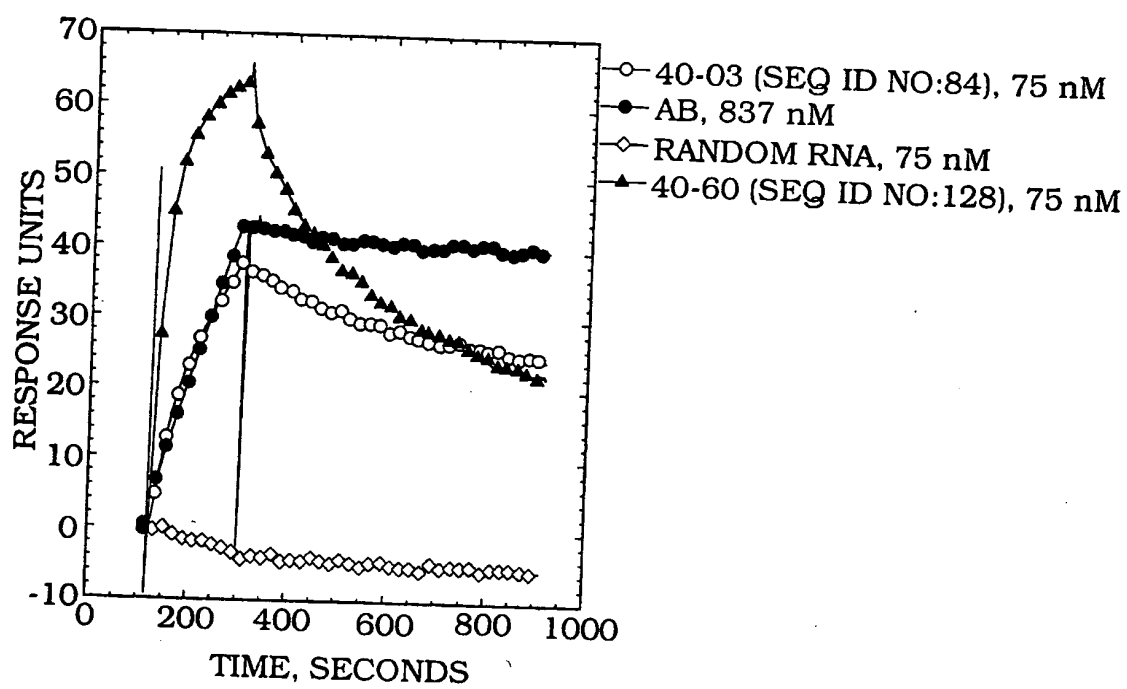


Figure 2

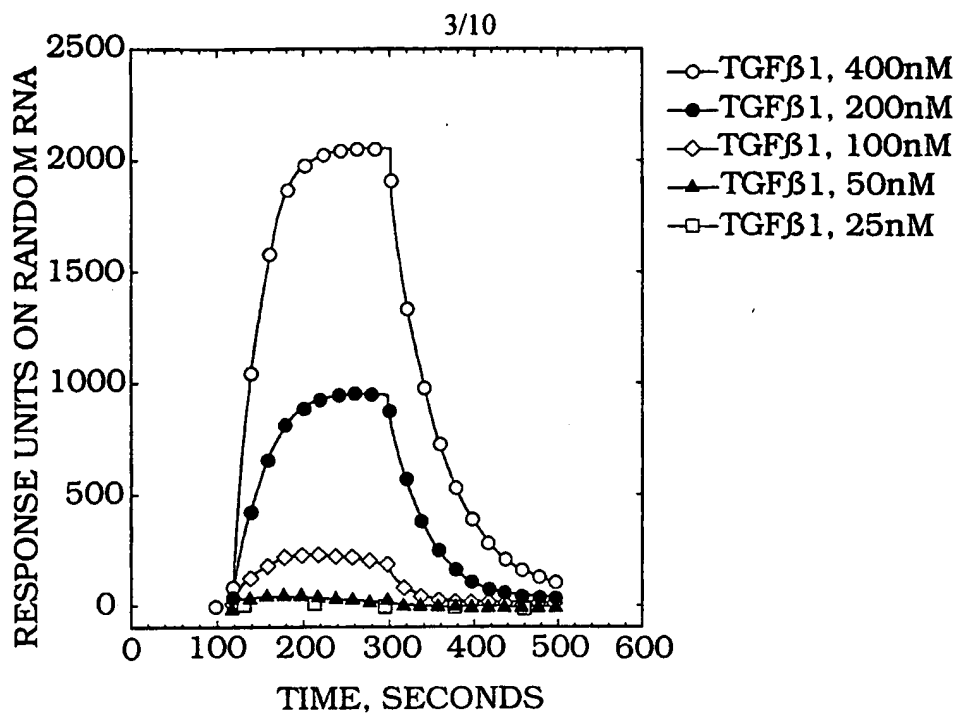


Figure 3A

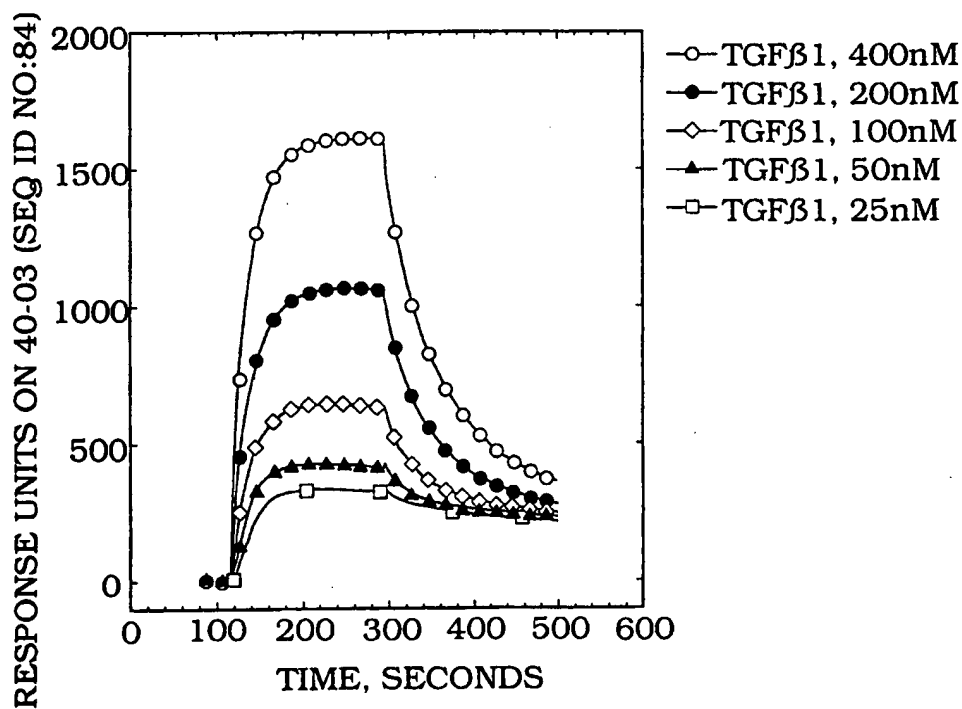


Figure 3B

4/10

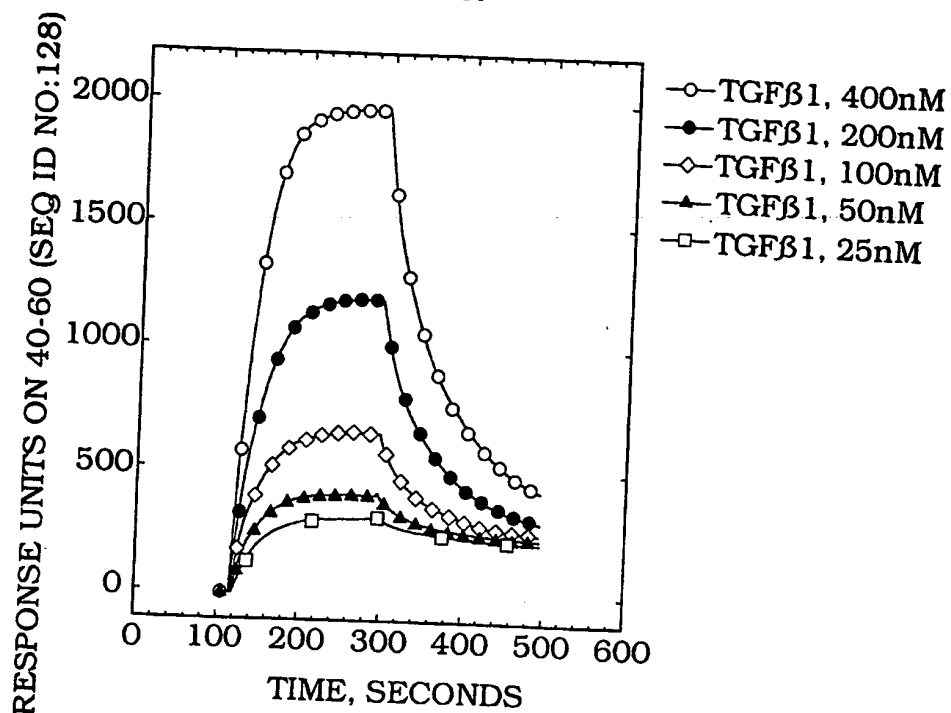


Figure 3C

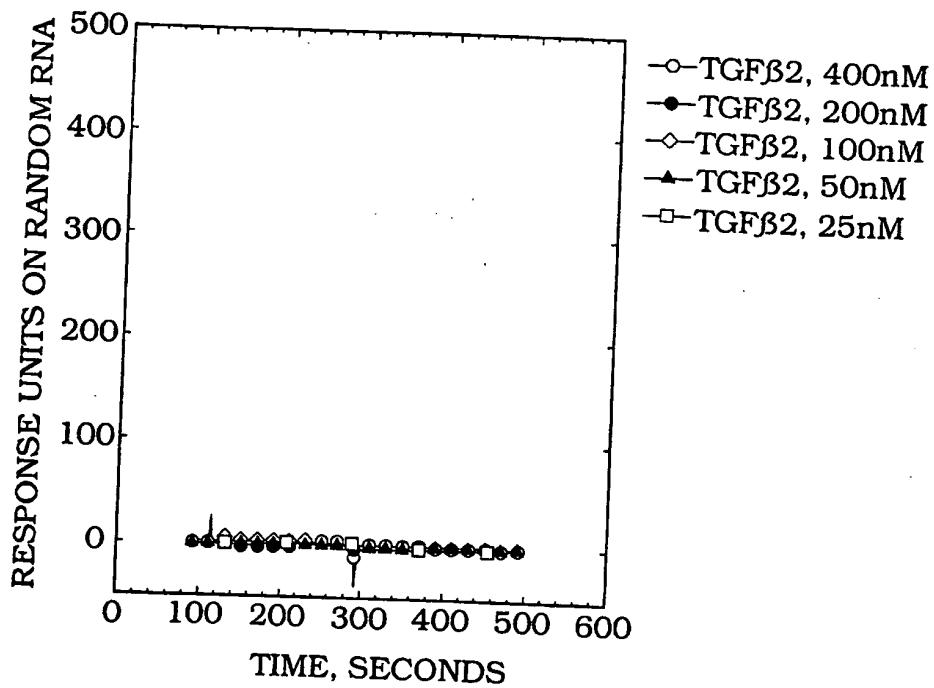


Figure 3D

5/10

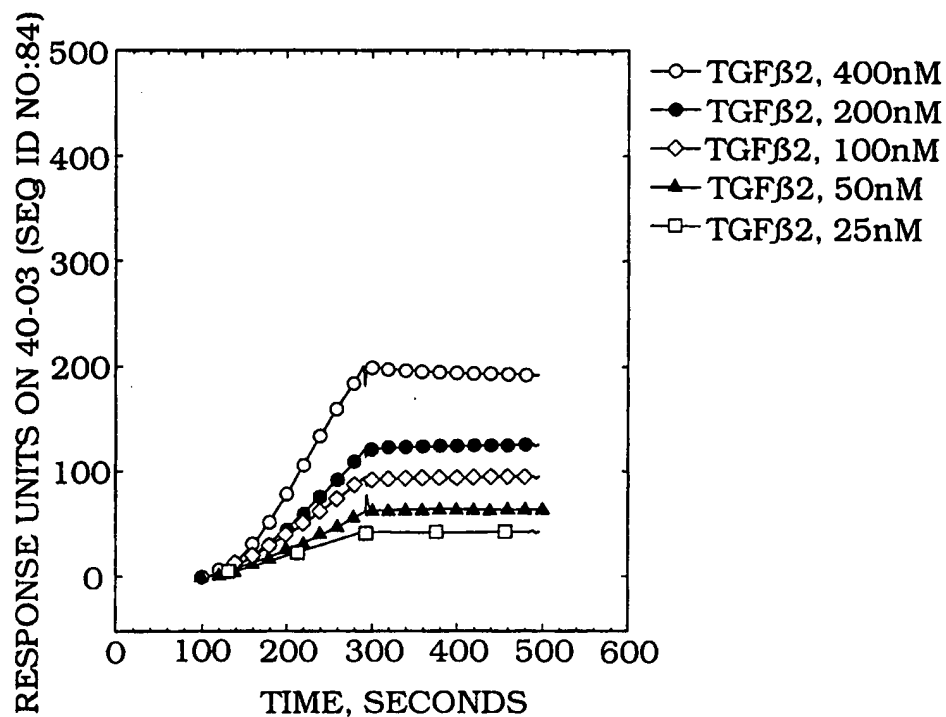


Figure 3E

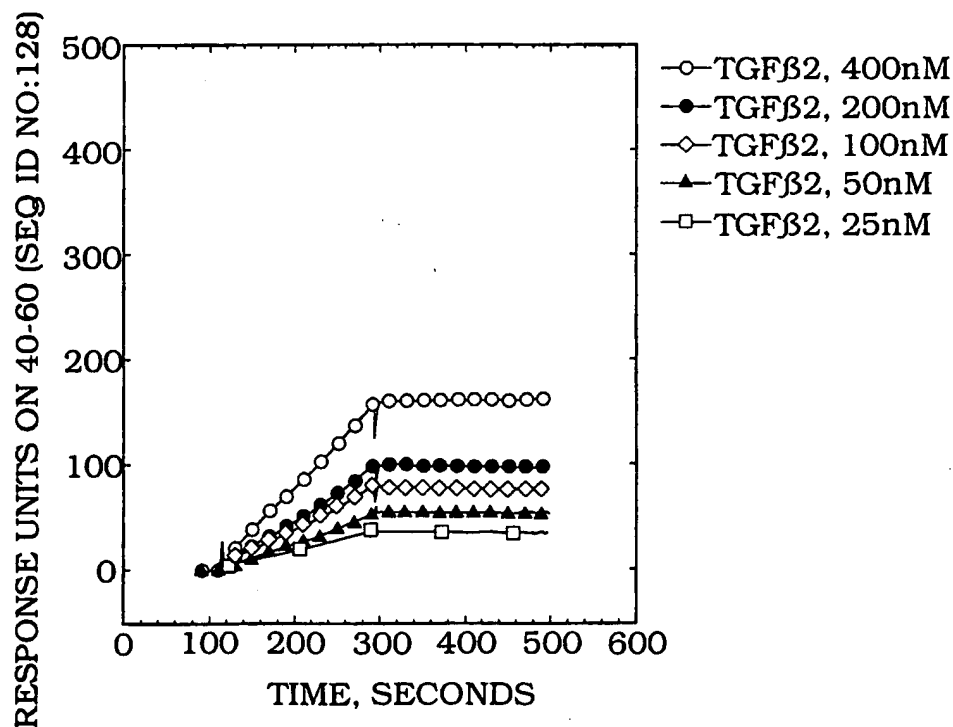


Figure 3F

6/10

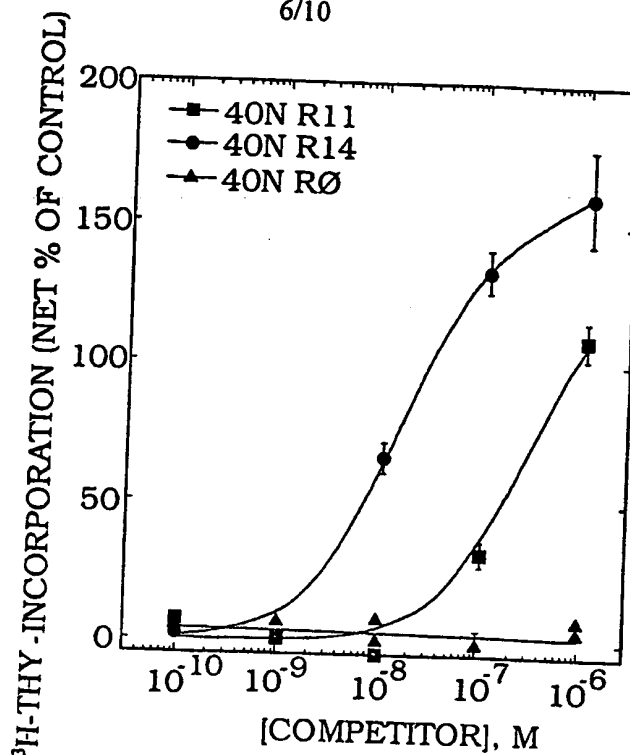


Figure 4A

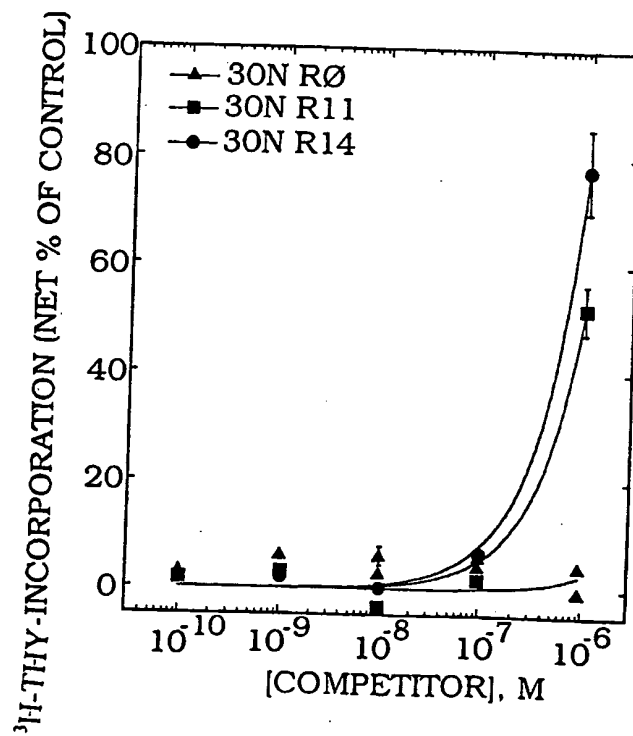


Figure 4B

7/10

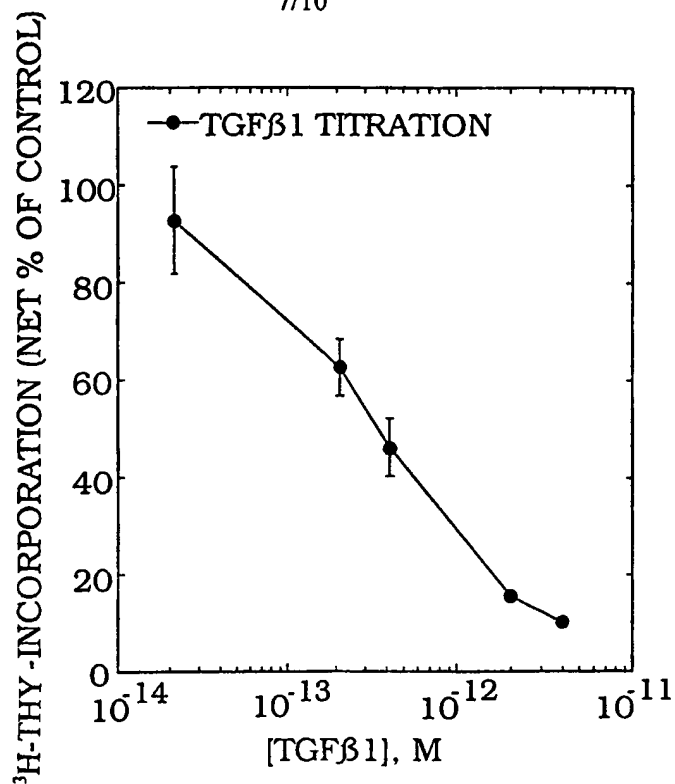


Figure 5A

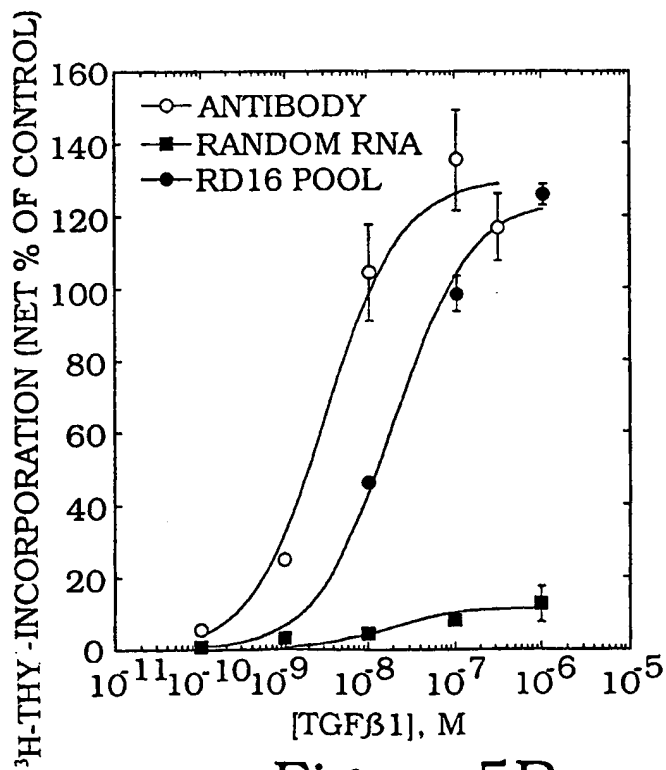


Figure 5B

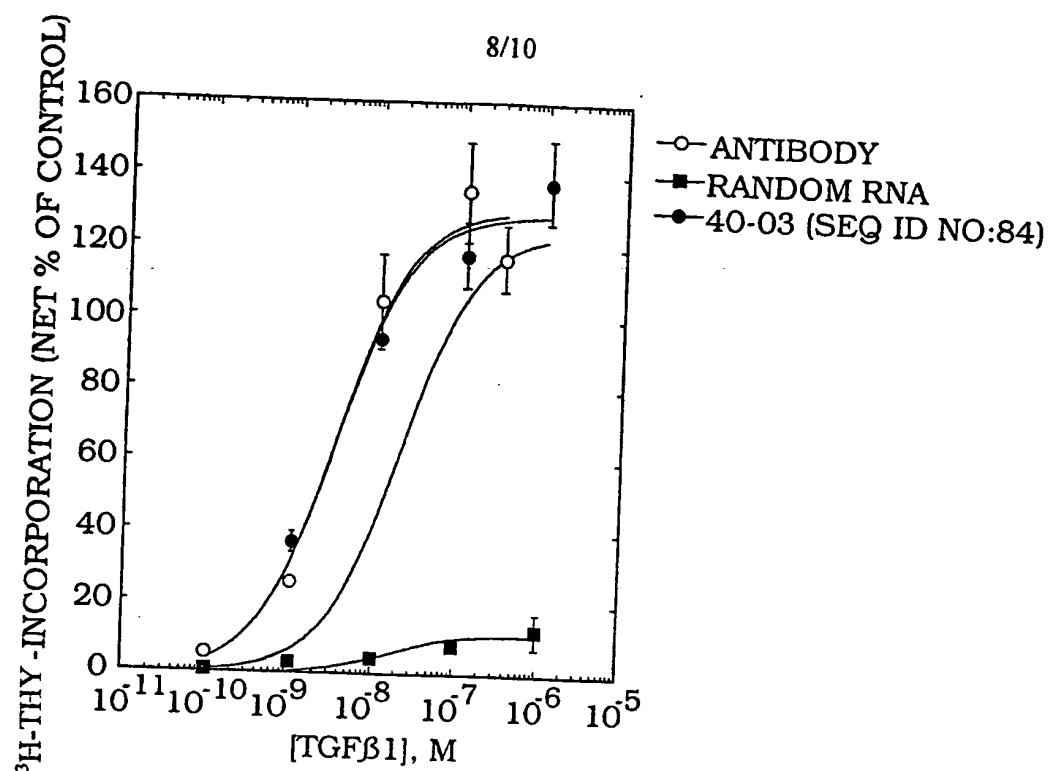


Figure 5C

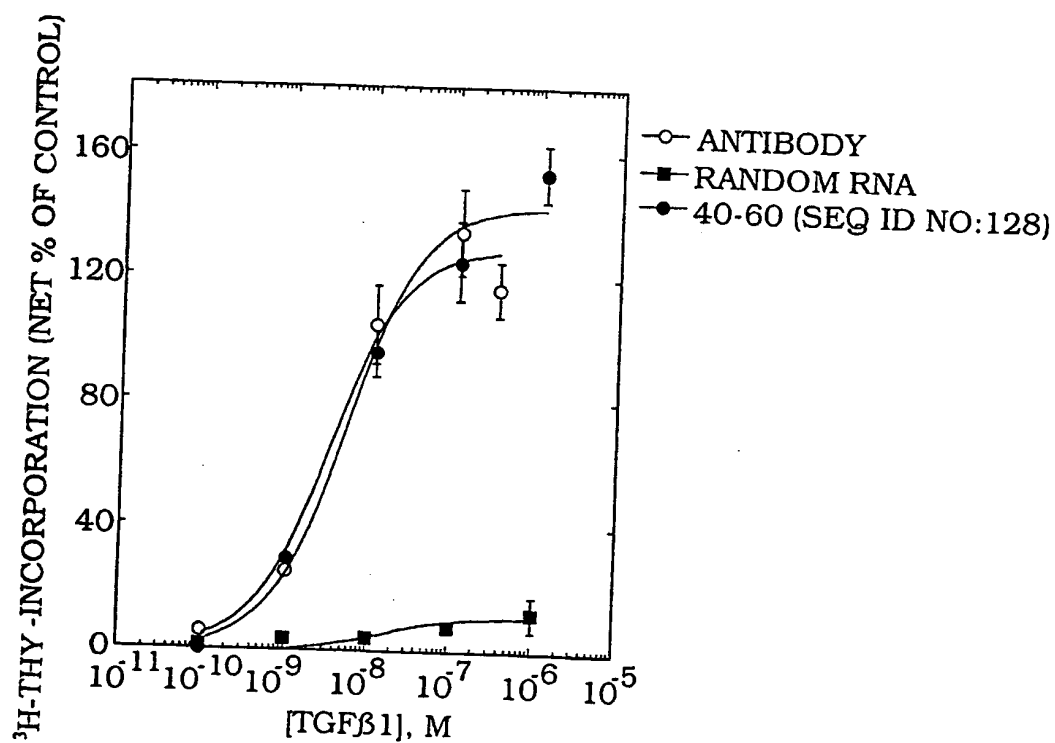


Figure 5D

9/10

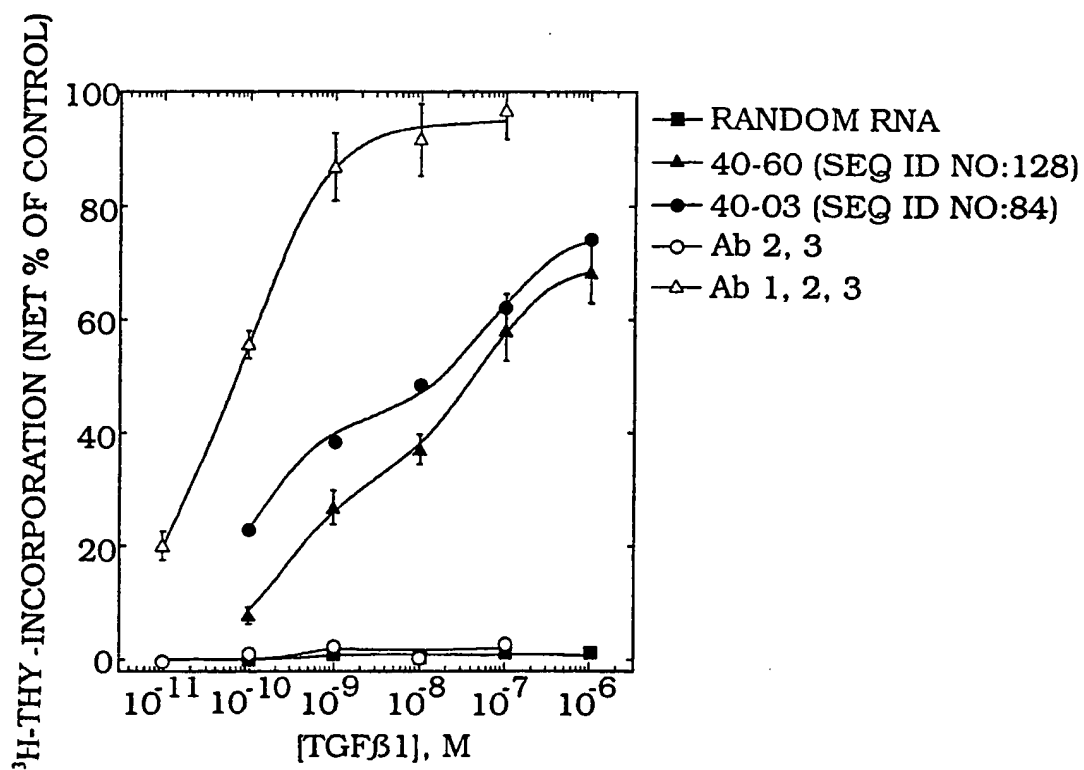


Figure 6

	S2	S1	S3	S1	S2	S3
40-03	gggaggacgatgcggggtta	ttggcggtcaacatccccg	attcttttcacgtcc	agacgactgccccga		
40-05	gggaggacgatgcgggttag	ggcggtcaacacccgctattcaaccttcg	ntttccc	cagacgactgccccga		
40-08	gggaggacgatgcgggttat	ggcggtcaacacccgctattcaaccttttcgctccc		cagacgactgccccga		
40-14	gggaggacgatg	cggcattat	ggcggtcaacatgccggttttcgattct	cattgtccagacgactgccccga		
40-16	gggaggacgatgcgggtta	ggcggtcaacacccgctattcaaccttttcgctccc		cagacgactgccccga		
40-19	gggaggacgatgcgggttag	ggcggtcaacacccgctattcaaccttttcgctccc		cagacgactgccccga		
40-23	gggaggacgatgcgggttag	ggcggtcaacacccgctattcaaccttttcgctccc		agac gactgccccga		
40-31	gggaggacgatgcgggttaa	ggcggtcaacacccgctattcaaccttttcgctccc		agacgactgccccga		
40-54	gggaggacgatgcgggttag	ggcggtcaacacccgctattcaaccttttcgctccc		agacgactgccccga		
40-56	gggaggacgatgcgggtta	ggcggtcaacacccgctattcaaccttttcgctccc		cagacgactgccccga		
40-60	gggaggacgatgcgggttat	ggcggtcaacacccgctattcaaccttttcgctccc		cagacgactgccccga		

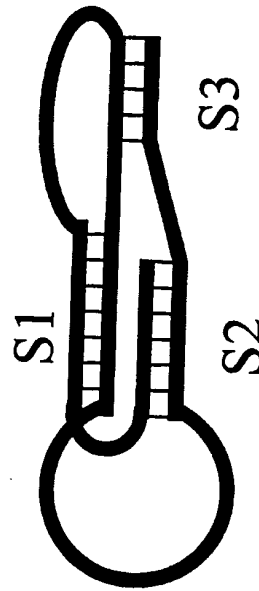


Fig. 7

SEQUENCE LISTING

- (1) GENERAL INFORMATION:
- (i) APPLICANT: LARRY GOLD
NIKOS PAGRATIS
 - (ii) TITLE OF THE INVENTION: HIGH AFFINITY TGF β NUCLEIC
ACID LIGANDS AND INHIBITORS
 - (iii) NUMBER OF SEQUENCES: 143
 - (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Swanson and Bratschun, L.L.C.
 - (B) STREET: 8400 East Prentice Avenue, Suite #200
 - (C) CITY: Denver
 - (D) STATE: Colorado
 - (E) COUNTRY: USA
 - (F) ZIP: 80111
 - (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Diskette, 3.5 inch, 1.44 Mb storage
 - (B) COMPUTER: IBM compatible
 - (C) OPERATING SYSTEM: MS DOS
 - (D) SOFTWARE: Word 97
 - (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER: PCT/US99/_____
 - (B) FILING DATE:
 - (C) CLASSIFICATION:
 - (vi) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: 09/046,247
 - (B) FILING DATE: 23-MARCH-1998
 - (C) CLASSIFICATION:
 - (vi) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: 08/458,424
 - (B) FILING DATE: 2-JUNE-1995
 - (C) CLASSIFICATION:
 - (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: 07/714,131
 - (B) FILING DATE: 10-JUNE-1991
 - (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: 07/536,428
 - (B) FILING DATE: 11-JUNE-1990
 - (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: 07/964,624
 - (B) FILING DATE: 21-OCTOBER-1992
 - (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: 08/117,991
 - (B) FILING DATE: 8-SEPTEMBER-1993
 - (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: 07/931,473
 - (B) FILING DATE: 17-AUGUST-1992
 - (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Barry Swanson
 - (B) REGISTRATION NUMBER: 33,215
 - (C) REFERENCE/DOCKET NUMBER: NEX 34.2/CIP-PCT
 - (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: (303) 793-3333
 - (B) TELEFAX: (303) 793-3433
- (2) INFORMATION FOR SEQUENCE ID NO: 1:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 71 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: DNA

- (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:
 GGGAGGACGA TCGGNNNNN NNNNNNNNN NNNNNNNNN NNNNNNNNN 50
 NNNNNCAGAC GACTCGCCCG A 71
- (2) INFORMATION FOR SEQUENCE ID NO: 2:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: DNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:
 GGGAGGACGA TCGGNNNNN NNNNNNNNN NNNNNNNNN NNNNNCAGAC 50
 GACTCGCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 3:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 51 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: DNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:
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 A 51
- (2) INFORMATION FOR SEQUENCE ID NO: 4:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 32 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: DNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:
 TAATACGACT CACTATAGGG AGGACGATGC GG 32
- (2) INFORMATION FOR SEQUENCE ID NO: 5:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 16 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: DNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:
 TCGGGCGAGT CGTCTG 16
- (2) INFORMATION FOR SEQUENCE ID NO: 6:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 51 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:
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A 51

(2) INFORMATION FOR SEQUENCE ID NO: 7:
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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:
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A 51

(2) INFORMATION FOR SEQUENCE ID NO: 8:
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(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:
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GACUCGCCCCG A 61

(2) INFORMATION FOR SEQUENCE ID NO: 9:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:
GGGAGGACGA UGCGGUGUCU UUAGCUUAGG UGAUCCUUC UGCCGACAGAC 50
GACUCGCCCCG A 61

(2) INFORMATION FOR SEQUENCE ID NO: 10:
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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
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CGACUCGCCCC GA 62

(2) INFORMATION FOR SEQUENCE ID NO: 11:

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 (A) LENGTH: 50 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
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- (2) INFORMATION FOR SEQUENCE ID NO: 12:
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 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:
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 GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 13:
 (i) SEQUENCE CHARACTERIZATION:
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 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
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 A 51
- (2) INFORMATION FOR SEQUENCE ID NO: 14:
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 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
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 (C) STRANDEDNESS: single
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 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

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A

50
51

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(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 49 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

GGGAGGACGA UGCGGGUCGU UUUUUUGGUC CUCCAGACGA CUCGCCCCGA

49

(2) INFORMATION FOR SEQUENCE ID NO: 17:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 51 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

GGGAGGACGA UGCGGGUUUU UAUAUUCGU UUGGCCAGAC GACUCGCCCCG

50

A

51

(2) INFORMATION FOR SEQUENCE ID NO: 18:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 52 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

GGGAGGACGA UGCGGGUCGA UCAUUUUUAG CCUCCCCAGA CGACUCGCCC

50

GA

52

(2) INFORMATION FOR SEQUENCE ID NO: 19:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 51 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

GGGAGGACGA UGCGGUGAGU UGAUCUUUUC GUCCCCAGAC GACUCGCCCCG

50

A

51

(2) INFORMATION FOR SEQUENCE ID NO: 20:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 60 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

- (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:
 GGGAGGACGA UGCGGUGCCU UUAGCUUAGG CAUUGCCUUC UGUGCAGACG 50
 ACUCGCCCCG A 60
- (2) INFORMATION FOR SEQUENCE ID NO: 21:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:
 GGGAGGACGA UGCGGCAAAA UUUUGGUCA AGCCGUCAUU GCCGCCAGAC 50
 GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 22:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 51 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:
 GGGAGGACGA UGCGGGUCCU UCUUUUUCC CUCCCCAGAC GACUCGCCCCG 50
 A 51
- (2) INFORMATION FOR SEQUENCE ID NO: 23:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:
 GGGAGGACGA UGCGGAUUU UUGUGAAGAC GUUUGCCGU UUGCCCAGAC 50
 GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 24:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 51 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:
 GGGAGGACGA UGCGGCGCAU CUUCUGUUU CUCCCCAGAC GACUCGCCCCG 50
 A 51
- (2) INFORMATION FOR SEQUENCE ID NO: 25:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 60 base pairs

(B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:
 GGGAGGACGA UGCGGGGAAU UUUUGGUAAA GCCGUAUGCC UGCCAGACG 50
 ACUCGCCCGA 60

(2) INFORMATION FOR SEQUENCE ID NO: 26:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:
 GGGAGGACGA UGCGGUCAUC UCUGGGAGUU AAGAUCAUUU GGCCGCAGAC 50
 GACUCGCCCG A 61

(2) INFORMATION FOR SEQUENCE ID NO: 27:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 51 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:
 GGGAGGACGA UGCGGGCAGC CUCUGAUUUU CUCCCCAGAC GACUCGCCCG 50
 A 51

(2) INFORMATION FOR SEQUENCE ID NO: 28:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 51 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:
 GGGAGGACGA UGCGGGUCGU GAUUUUCGUU CUGCCCAGAC GACUCGCCCG 50
 A 51

(2) INFORMATION FOR SEQUENCE ID NO: 29:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 52 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:
 GGGAGGACGA UGCGGGUCGU AUUUUUUCCG CCUCCCCAGA CGACUCGCCC 50
 GA 52

- (2) INFORMATION FOR SEQUENCE ID NO: 30:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 59 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:
 GGGAGGACGA UGCGGUCCUC AGCCUCAC UUAUUAUCCU CCCAGACGA 50
 CUCGCCCCGA 59
- (2) INFORMATION FOR SEQUENCE ID NO: 31:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 51 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:
 GGGAGGACGA UCGGGGUCUA CUUGUUUAC CUCCCCAGAC GACUCGCCCCG 50
 A 51
- (2) INFORMATION FOR SEQUENCE ID NO: 32:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 51 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:
 GGGAGGACGA UCGGCGGAU UUUUCGUCU UUGGCCAGAC GACUCGCCCCG 50
 A 51
- (2) INFORMATION FOR SEQUENCE ID NO: 33:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 61 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:
 GGGAGGACGA UCGGUGUCU AUAGCCUUGA UUAUAUCAUC UGCCGCAGAC 50
 GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 34:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 51 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:

(D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

GGGAGGACGA UGCGGCGAUU CCUCUUUUA CUCCCCAGAC GACUCGCCCCG 50
A 51

(2) INFORMATION FOR SEQUENCE ID NO: 35:

(i) SEQUENCE CHARACTERIZATION:

(A) LENGTH: 51 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

(D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

GGGAGGACGA UGCGGUCCCA UUUUUCUCCU CUCCCCAGAC GACUCGCCCCG 50
A 51

(2) INFORMATION FOR SEQUENCE ID NO: 36:

(i) SEQUENCE CHARACTERIZATION:

(A) LENGTH: 51 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

(D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

GGGAGGACGA UGCGGGUUA UUUUUGUCCU CUGGCCAGAC GACUCGCCCCG 50
A 51

(2) INFORMATION FOR SEQUENCE ID NO: 37:

(i) SEQUENCE CHARACTERIZATION:

(A) LENGTH: 56 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

(D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

GGGAGGACGA UGCGGUUUUU UUCUUUUUUC UUUUUUCCG CAGACGACUC 50
GCCCCA 56

(2) INFORMATION FOR SEQUENCE ID NO: 38:

(i) SEQUENCE CHARACTERIZATION:

(A) LENGTH: 50 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE

(D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

GGGAGGACGA UGCGGUCGUC UUUGUUUUUC UCCCCAGACG ACUCGCCCCG 50

(2) INFORMATION FOR SEQUENCE ID NO: 39:

(i) SEQUENCE CHARACTERIZATION:

(A) LENGTH: 61 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

- (D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:
GGGAGGACGA UGCGGUGUCU AUAGCCUUGA UUACAUCauc UGCCGCAGAC 50
GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 40:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:
GGGAGGACGA UGCGGUGCCU UUAGCUUAGG CAUUGCCUUC UGCCGCAGAC 50
GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 41:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:
GGGAGGACGA UGCGGUGUCU AUAGCUUGAU UUUUAAUUUC UGCCGCAGAC 50
GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 42 :
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:
GGGAGGACGA UGCGGUUUUA UUUUCUUCGU CUGGCCAGAC GACUCGCCCCG 50
A 51
- (2) INFORMATION FOR SEQUENCE ID NO: 43:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 73 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:
GGGAGGACGA UGCGGGAUGA ACCGAACCGA GGUUAAGGUG CCAGAGUAGA 50
CGCUCAUCAG ACGACUCGCC CGA 73
- (2) INFORMATION FOR SEQUENCE ID NO: 44:

- (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 51 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:
 GGGAGGACGA UGCGGUCGUC UAUUUUUUCC CUCCCCAGAC GACUCGCCCCG 50
 A 51
- (2) INFORMATION FOR SEQUENCE ID NO: 45:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 51 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:
 GGGAGGACGA UGCGGCUUUC GUCUGUUUUC CUGCCCAGAC GACUCGCCCCG 50
 A 51
- (2) INFORMATION FOR SEQUENCE ID NO: 46:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:
 GGGAGGACGA UGCGGUGUCU UUAGCCUAGG UGAUUCCUUC UGCCGCAGAC 50
 GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 47:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 60 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:
 GGGAGGACGA UGCGGCCUUG UUUUCUUUUU UCUUUUUUCA CCCCCAGACG 50
 ACUCGCCCCGA 60
- (2) INFORMATION FOR SEQUENCE ID NO: 48:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

GGGAGGACGA UGCGGUGUCU UUAGCCCAGG UGAUCCUUC UGCCGCAGAC
GACUCGCCCC A

50
61

(2) INFORMATION FOR SEQUENCE ID NO: 49:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 61 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

GGGAGGACGA UGCGGUUAAAC CGUAAAGACG GCAUGAUGUA GUCCGCAGAC
GACUCGCCCC A

50
61

(2) INFORMATION FOR SEQUENCE ID NO: 50:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 61 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

GGGAGGACGA UGCGGUUUUU UUAGCUUAGG UGAUCCUUC NNCCUCAGAC
GACUCGCCCC A

50
61

(2) INFORMATION FOR SEQUENCE ID NO: 51:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 61 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

GGGAGGACGA UGCGGUGCCU UUAGCUUAGG CUUUGCCUUC UGCCGCAGAC
GACUCGCCCC A

50
61

(2) INFORMATION FOR SEQUENCE ID NO: 52:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 58 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

GGGAGGACGA UGCGGCGGAA UUUUGUUGA GCCGUAUGCC GCCAGACGAC
UCGCCCGA

50
58

(2) INFORMATION FOR SEQUENCE ID NO: 53:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 61 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

- (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:
 GGGAGGACGA UGCGGUGCCU UUAGCUUAGG UGAUCCUUC UGCCGAGAC 50
 GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 54:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:
 GGGAGGACGA UGCGGUGUCU UUAGCCUAGG UGAUCCUUC UGCCGAGAC 50
 GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 55:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:
 GGGAGGACGA UGCGGUGUCU AUAGCCUGAU UUUUAAUCUC UGCCGAGAC 50
 GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 56:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:
 GGGAGGACGA UGCGGUUGAC CGUUAAGACG GCAUGAUGUG GUCCGAGAC 50
 GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 57:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:
 GGGAGGACGA UGCGGUGCCU UUAGCUUAGG CAUUGCCUUC UGCCGAGAC 50
 GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 58:
 (i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:
GGGAGGACGA UGCGGUGCCU UUAGCUUAGG CUUUGCCUUC UGCCGCAGAC 50
GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 59:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:
GGGAGGACGA UGCGGUUAAAC CNUAAUACG GCUUGANUUC UGCCGCAGAC 50
GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 60:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:
GGGAGGACGA UGCGGUGCCU UUAGCUUAGG CAUUGCCUUC UGCCGCAGAC 50
GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 61:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:
GGGAGGACGA UGCGGUUAAAC CGUAAAGACG GCAUGAUGUU UGCCGCAGAC 50
GACUCGCCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 62:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 61 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:
GGGAGGACGA UGCGGUUGGC AUUGAAAGAG GCGUCAUAUG UGCCGCAGAC 50

GACUCGCCCCG A

61

(2) INFORMATION FOR SEQUENCE ID NO: 63:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 62 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

GGGAGGACGA UGCGGCCUUU CUUUCUUUUU AUUUUCUUC CCUCCCCAGA 50
 CGACUCGCCC GA 62

(2) INFORMATION FOR SEQUENCE ID NO: 64:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 61 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

GGGAGGACGA UGCGGUGCCU UUAGCCUAGA CCUUGUCUUC UGCCGCAGAC 50
 GACUCGCCCCG A 61

(2) INFORMATION FOR SEQUENCE ID NO: 65:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 61 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

GGGAGGACGA UGCGGUGUCU UUAGCCUAGG UGAUUCUUC UGCCGCAGAC 50
 GACUCGCCCCG A 61

(2) INFORMATION FOR SEQUENCE ID NO: 66:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 61 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

GGGAGGACGA UGCGGUGUCU UUAGCCUAGG UGAUUCUUC UGCCGCAGAC 50
 GACUCGCCCCG A 61

(2) INFORMATION FOR SEQUENCE ID NO: 67:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 71 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

- (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:
 GGGAGGACGA UGCGGACCGG UAAGGGCACU GCAGGAACAC AAUCCCCUAU 50
 GCGACCAGAC GACUCGCCCG A 71
- (2) INFORMATION FOR SEQUENCE ID NO: 68 :
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 60 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:
 GGGAGGACGA UGCGGGGAU UUUGGUAU GCGGUAUGCC UGCCAGACG 50
 ACUCGCCCGA 60
- (2) INFORMATION FOR SEQUENCE ID NO: 69:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 60 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:
 GGGAGGACGA UGCGGUGGCA UUGAAAGAGA UCGCAUACCU UGCCAGACG 50
 ACUCGCCCGA 60
- (2) INFORMATION FOR SEQUENCE ID NO: 70:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:
 GGGAGGACGA UGCGGUGUCU AUAGCCUUGA UUACAUCAUC UGCCUCAGAC 50
 GACUCGCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 71:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:
 GGGAGGACGA UGCGGUGUCU UUAGCCUAGG UGAUCCUUC UGCCUCAGAC 50
 GACUCGCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 72:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs

(B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:
 GGGAGGACGA UGCGGUGCCU UUAGCUUAUG CAUUGCCUUC UGCCGCAGAC 50
 GACUCGCCCC A 61

(2) INFORMATION FOR SEQUENCE ID NO: 73:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 62 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:
 GGGAGGACGA UGCGGUGCCU UUAGCUUAGG CAUUGCCUUC CUGCCGCAGA 50
 CGACUCGCCC GA 62

(2) INFORMATION FOR SEQUENCE ID NO: 74:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:
 GGGAGGACGA UGCGGUGUCU UUGGCCUAGG UGAUCCUUC UGCCGCAGAC 50
 GACUCGCCCC A 61

(2) INFORMATION FOR SEQUENCE ID NO: 75:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:
 GGGAGGACGA UGCGGUGUCU UUAGCUUAGG UGAUCCUUC UGCCGCAGAC 50
 GACUCGCCCC A 61

(2) INFORMATION FOR SEQUENCE ID NO: 76:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 61 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:
 GGGAGGACGA UGCGGUGUCU UUAGCCUAGG UGAUCCUUC UGCCGCAGAC 50
 GACUCGCCCC A 61

- (2) INFORMATION FOR SEQUENCE ID NO: 77:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 59 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:
 GGGAGGACGA UGCGGUGCCU UUAGCUUAGG CAUUGCCUUG CCGCAGACGA 50
 CUCGCCCCGA 59
- (2) INFORMATION FOR SEQUENCE ID NO: 78:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 62 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:
 GGGAGGACGA UGCGGGGUCU UUUUUUUUU GUUUUUCUCU GUGCCCCAGA 50
 CGACUCGCCC GA 62
- (2) INFORMATION FOR SEQUENCE ID NO: 79:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 61 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:
 GGGAGGACGA UGCGGUUAC CGUAAAGACA GCAUGAUGUA GUCUGCAGAC 50
 GACUCGCCCC A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 80:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 60 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:
 GGGAGGACGA UGCGGUUUUU UUCUUUUCCU UCCUUUUCUU ACCGCAGACG 50
 ACUCGCCCCA 60
- (2) INFORMATION FOR SEQUENCE ID NO: 81:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 61 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:
GGGAGGACGA UGCGGUUAAC CGUAAAGACG GCAUGAUGUU GUCCGCAGAC 50
GACUCGCCCG A 61
- (2) INFORMATION FOR SEQUENCE ID NO: 82:
- (i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:
GGGAGGACGA UGCGGGGAU UUUGGUAAA GCCGUAUGCC UGCCAGACG 50
ACUCGCCCGA 60
- (2) INFORMATION FOR SEQUENCE ID NO: 83:
- (i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:
GGGAGGACGA UGCGGGCCAA GGUUACGCCG UCGGACCUG CUGCCAACAU 50
CCUCCCCAGA CGACUCGCCG GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 84:
- (i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 70 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:
GGGAGGACGA UGCGGGGUU AUUGGCGUC AACAUCCCCG AUUCUUUUA 50
CGUCCAGACG ACUCGCCCGA 70
- (2) INFORMATION FOR SEQUENCE ID NO: 85:
- (i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:
GGGAGGACGA UGCGGAUGCC UUUGCCUUC AGGGUGUAU UCCUUGAUCU 50
GUCCGCAGAC GACUCGCCG A 71
- (2) INFORMATION FOR SEQUENCE ID NO: 86:
- (i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:
 GGGAGGACGA UGCGGAACAA GGUUACGCCG UCGGACCCUG CUGCCAACAU 50
 CCUCCCCAGA CGACUCGCCC GA 72

(2) INFORMATION FOR SEQUENCE ID NO: 87:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 71 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:
 GGGAGGACGA UGCGGUUAGG GGCGUCAACA CCGCUAUCAU AAUUUUCGCC 50
 UUCCCCAGAC GACUCGCCCC A 71

(2) INFORMATION FOR SEQUENCE ID NO: 88:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 71 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:
 GGGAGGACGA UGCGGCGCAA GGUUACGCCG UCGGACCCUG CUGCCAACAU 50
 CCUCCCCAGAC GACUCGCCCC A 71

(2) INFORMATION FOR SEQUENCE ID NO: 89:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 69 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:
 GGGAGGACGA UGCGGUGCCU UUAGUCUGAA UCUUCUACCA UGAUUCUCUG 50
 CCGCAGACGA CUCGCCCCA 69

(2) INFORMATION FOR SEQUENCE ID NO: 90:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 71 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:
 GGGAGGACGA UGCGGGACCC UUGUCUGCGA UUCAACUCGU AGGUUUUCUC 50
 ACGUGCAGAC GACUCGCCCC A 71

- (2) INFORMATION FOR SEQUENCE ID NO: 91:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 72 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

GGGAGGACGA UGCGGAGCAA GGUUACGAGG UCGGACCCUG CUGCCAACAU	50
CCUCCCCAGA CGACUCGCCC GA	72
- (2) INFORMATION FOR SEQUENCE ID NO: 92:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 71 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

GGGAGGACGA UGCGGCAUUA UGGCGUCAAC AUGCCGGUUU UCGAUUCUA	50
UUGUCCAGAC GACUCGCCCC A	71
- (2) INFORMATION FOR SEQUENCE ID NO: 93:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 70 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

GGGAGGACGA UGCGGCUCUA ACUUCUUUUU CGCCUGUGUG UUUUCUUUUU	50
GCUGCAGACG ACUCGCCCCA	70
- (2) INFORMATION FOR SEQUENCE ID NO: 94:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 70 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

GGGAGGACGA UGCGGUUAGG GCGUCAACA CCGCUAUAC AUCUUUCGCC.	50
UCCCCAGACG ACUCGCCCCA	70
- (2) INFORMATION FOR SEQUENCE ID NO: 95:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 69 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:
 GGGAGGACGA UGCGGGGUCG UUUUGUUUUU GUUUUUUGUA GCCCCGUCAU 50
 CCCCAGACGA CUCGCCCCGA 69
- (2) INFORMATION FOR SEQUENCE ID NO: 96:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 71 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:
 GGGAGGACGA UGCGGUUAGC GCGAGUUCAA CACCGCAUGU GAUUCUUUCG 50
 CCUCCAGAC GACUCGCCCC A 71
- (2) INFORMATION FOR SEQUENCE ID NO: 97:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 72 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:
 GGGAGGACGA UGCGGUACAA GGUUACGCCG UCGGACCCUG CUGCCAACAU 50
 CCUCCCCAGA CGACUCGCCC GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 98:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 70 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:
 GGGAGGACGA UGCGGGACCC UGUCUGCGA UUCAACUCGU AGGUCUUCUC 50
 CGUGCAGACG ACUCGCCCCA 70
- (2) INFORMATION FOR SEQUENCE ID NO: 99:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 69 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:
 GGGAGGACGA UGCGGUUAGG GGCGUCAACA CCGCUAUUAC AAUUUUCGU 50
 UCCCAGACGA CUCGCCCCGA 69
- (2) INFORMATION FOR SEQUENCE ID NO: 100:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 69 base pairs
 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:
 GGGAGGACGA UGCGGUUAGG GGCGUCAACA CCGCUAUUAC AAUCUUCGCU 50
 UCCCAGACGA CUCGCCCCGA 69

(2) INFORMATION FOR SEQUENCE ID NO: 101:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 70 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:
 GGGAGGACGA UGCGGUUAUG GGCGUCAACA CCGCUAUUAC AACUUUCGCU 50
 UUCCCAGACG ACUCGCCCCGA 70

(2) INFORMATION FOR SEQUENCE ID NO: 102:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 72 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:
 GGGAGGACGA UGCGGUGUCG AUCGUUUGCU GUUUGAUUUC UUUUGUCCCU 50
 CCCGUGCAGA CGACUCGCCC GA 72

(2) INFORMATION FOR SEQUENCE ID NO: 103:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 70 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:
 GGGAGGACGA UGCGGUUAGG GGCGUCAACA UCGCUAUUAC AAUCUUCGCC 50
 UUCCCAGACG ACUCGCCCCGA 70

(2) INFORMATION FOR SEQUENCE ID NO: 104:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 70 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:
 GGGAGGACGA UGCGGUUAGG GGCGUCAACA CCGCUAUUAC AACUUUCGCC 50
 UCACCAGACG ACUCGCCCCGA 70

- (2) INFORMATION FOR SEQUENCE ID NO: 105:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 71 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:
 GGGAGGACGA UGCGGGACCC UUUUCUGCGA UUCAACUCGU ACGUCUUCUC 50
 ACGUGCAGAC GACUCGCCCG A 71
- (2) INFORMATION FOR SEQUENCE ID NO: 106:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 68 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:
 GGGAGGACGA UGCGGUUAAG GGCGUCAACA CCGCUAUUAA ACUUUCGCUU 50
 CCCAGACGAC UCGCCCGA 68
- (2) INFORMATION FOR SEQUENCE ID NO: 107:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 68 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:
 GGGAGGACGA UGCGGUUAUG GGCGUCAACA CCGCUAUUAC AACUUUCGCC 50
 UCCAGACGAC UCGCCCGA 68
- (2) INFORMATION FOR SEQUENCE ID NO: 108:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 72 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:
 GGGAGGACGA UGCGGAGCAA GGUUACGCCG UCGGACCCUG CUGCCAACAU 50
 CCUCCCCAGA CGACUCGCCG GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 109:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 63 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:
GGGAGGACGA UGCGGGUCAA GGUUACGCCG UCGGACCCUA CUGCCCCCAG 50
ACGACUCGCC CGA 63
- (2) INFORMATION FOR SEQUENCE ID NO: 110:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:
GGGAGGACGA UGCGGCUCU AUAUUAUGU UAUUGUUUUU UUCUCCAGC 50
UUGCCCCAGA CGACUCGCCC GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 111:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:
GGGAGGACGA UGCGGAGAU AUAUCAGCG GUGGACGGGG UGCCGGUACU 50
CCGCCAGAC GACUCGCCCC A 71
- (2) INFORMATION FOR SEQUENCE ID NO: 112:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 69 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:
GGGAGGACGA UGCGGUGCCU UUAGCCUAG UGAUCUAUU CAGCUUUCUG 50
CCGCAGACGA CUCGCCCCA 69
- (2) INFORMATION FOR SEQUENCE ID NO: 113:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:
GGGAGGACGA UGCGGCCCAA GGUUACGCCG UCGGACCCUA CUGCCAACUU 50
CCUCCCCAGA CGACUCGCCC GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 114:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 70 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

- (D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:
GGGAGGACGA UGCGGUGCCU UUAGCCUGAG UAUACUGAUG UAUAUUCUCU 50
GCCGCAGACG ACUCGCCCGA 70
- (2) INFORMATION FOR SEQUENCE ID NO: 115:
- (i) SEQUENCE CHARACTERIZATION:
- (A) LENGTH: 70 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:
GGGAGGACGA UGCGGUAGCG CGAGUUCAAC ACCGCAUGUG ACUCUUUCGC 50
CUCCAGACG ACUCGCCCGA 70
- (2) INFORMATION FOR SEQUENCE ID NO: 116:
- (i) SEQUENCE CHARACTERIZATION:
- (A) LENGTH: 72 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:
GGGAGGACGA UGCGGAUCCU UUUUUUAGCU UUUUUCUUUU UCCUGCCCCA 50
CUCCCCAGA CGACUCGCCC GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 117:
- (i) SEQUENCE CHARACTERIZATION:
- (A) LENGTH: 72 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:
GGGAGGACGA UGCGGUGCAA GGUUACGCCG UCGGACCCUG CUGCCAACAU 50
CCUCCCCAGA CGACUCGCCC GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 118:
- (i) SEQUENCE CHARACTERIZATION:
- (A) LENGTH: 69 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:
GGGAGGACGA UGCGGGGCGU UUUCUUUAG UACUUUUUG UUUCGCUCCC 50
CCCCAGACGA CUCGCCCGA 69

(2) INFORMATION FOR SEQUENCE ID NO: 119:

- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 69 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

GGGAGGACGA UGCGGUGCCU UUAGUCUGAA UCUUACCAUG CGAUUUUCUG	50
CCGCAGACGA CUCGCCCGA	69

(2) INFORMATION FOR SEQUENCE ID NO: 120:

- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 72 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

GGGAGGACGA UGCGGAACAA GGUUACUCCG UCGGACCCUG CUGCCAACAU	50
CCUCCCCAGA CGACUCGCCG GA	72

(2) INFORMATION FOR SEQUENCE ID NO: 121:

- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 71 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

GGGAGGACGA UGCGGGACUC UUGUCUGCGA UUCAACUCGU AGGUCUUCUC	50
ACGUGCAGAC GACUCGCCCG A	71

(2) INFORMATION FOR SEQUENCE ID NO: 122:

- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 70 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

GGGAGGACGA UGCGGUUAGG GGCGUCAACA CCGCUAUCAU AACUUUCGCU	50
UCCCCAGACG ACUCGCCCGA	70

(2) INFORMATION FOR SEQUENCE ID NO: 123:

- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 69 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULAR TYPE: RNA
- (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:
GGGAGGACGA UGCGGUUAGG GCGUCAACA CCGCUAUUCA ACCUUCGCUU
CCCCAGACGA CUCGCCCGA

50
69

(2) INFORMATION FOR SEQUENCE ID NO: 124:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 69 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:
GGGAGGACGA UGCGGUUAGG GCGUCAACAC CGCUAUUACA ACUUCGCCU
CCCCAGACGAC UCGCCCCA

50
69

(2) INFORMATION FOR SEQUENCE ID NO: 125:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 51 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125:
GGGAGGACGA UGCGGGGUGU CGUCUUUCAA CCCUCAGAC GACUCGCCCG
A

50
51

(2) INFORMATION FOR SEQUENCE ID NO: 126:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 70 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:
GGGAGGACGA UGCGGUUAUG GCGUCAACA CCGCUAUUAC AACUUUCGCC
UCCCCAGACG ACUCGCCCGA

50
70

(2) INFORMATION FOR SEQUENCE ID NO: 127:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 72 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: RNA

(ix) FEATURE:

- (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:
GGGAGGACGA UGCGGCCCAA GGUUACGCCG UCGGACCCUG CUGCAAACAU
CCUCCCCAGA CGACUGCCCC GA

50
72

(2) INFORMATION FOR SEQUENCE ID NO: 128:

(i) SEQUENCE CHARACTERIZATION:

- (A) LENGTH: 71 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:
 GGGAGGACGA UGCGGUUAUG GGCGUCAACA CCGCUAUUAC AGUUUUCGCC 50
 UCCCCAGAC GACUCGCCCCG A 71

(2) INFORMATION FOR SEQUENCE ID NO: 129:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 70 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:
 GGGAGGACGA UGCGGUUAGG GGCGUCAACA CCGCUAUUAC AAUCUUCGCU 50
 UUCCAGACG ACUCGCCCCG 70

(2) INFORMATION FOR SEQUENCE ID NO: 130:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 72 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:
 GGGAGGACGA UGCGGGCCAA GGUUACGCCG UCGGACCCUG CUGCCAACAU 50
 CUUCCCCAGA CGACUCGCCC GA 72

(2) INFORMATION FOR SEQUENCE ID NO: 131:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 70 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:
 GGGAGGACGA UGCGGUUAGG GGCGUCAACA CCGCUAUUAC AAUCUUCGUC 50
 UUCCAGACG ACUCGCCCCG 70

(2) INFORMATION FOR SEQUENCE ID NO: 132:
 (i) SEQUENCE CHARACTERIZATION:
 (A) LENGTH: 72 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULAR TYPE: RNA
 (ix) FEATURE:
 (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132:
 GGGAGGACGA UGCGGGUCAA GUUACGCCG UCGGACCCUG CUGCCAACAU 50
 CCUCCCCAGA CGACUCGCCC GA 72

- (2) INFORMATION FOR SEQUENCE ID NO: 133:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 72 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133:
 GGGAGGACGA UGCGGUUCAA GGUUACGCCG UCGGACCCUG CUGCCAACAU 50
 CCUCCCCAGA CGACUCGCCC GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 134:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 72 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134:
 GGGAGGACGA UCGGGCUCAA GGUUACGCCG UCGGACCCUG CUGCCAACAU 50
 CCUCCCCAGA CGACUCGCCC GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 135:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 70 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:
 GGGAGGACGA UGCGGUUAGG GGCUCUACA CCGCUAUUAC AUUCUUCGCC 50
 UCCCCAGACG ACUCGCCCCGA 70
- (2) INFORMATION FOR SEQUENCE ID NO: 136:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 72 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136:
 GGGAGGACGA UGCGGCACAA AGUUACGCCG UAGGACCCUG CUGCCAACAU 50
 CCUCCCCAGA CGACUCGCCC GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 137:
- (i) SEQUENCE CHARACTERIZATION:
 - (A) LENGTH: 72 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULAR TYPE: RNA
 - (ix) FEATURE:
 - (D) OTHER INFORMATION: All pyrimidines are 2'-F modified

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:
GGGAGGACGA UGCGGGGAUG GUCAGUUUCG GUUUUUAUA UGUUUUAUUU 50
CCCCCCCAGA CGACUCGCCC GA 72
- (2) INFORMATION FOR SEQUENCE ID NO: 138:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 66 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:
GGGAGGACGA UGCGGUUAGU ACUUUUGUUU CUUUUUCUUU GCCUGGUCCC 50
CAGACGACUC GCCCGA 66
- (2) INFORMATION FOR SEQUENCE ID NO: 139:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 70 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:
GGGAGGACGA UGCGGUUAGG GGCGUCAACA CCGCUAUUAC AACUUUCGCU 50
UCCCCAGACG ACUCGCCCCGA 70
- (2) INFORMATION FOR SEQUENCE ID NO: 140:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 69 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:
GGGAGGACGA UGCGGCUUCU UUUUCUUCUU UUCUUUAUGU CUUCUUAUG 50
CCGCAGACGA CUCGCCCCGA 69
- (2) INFORMATION FOR SEQUENCE ID NO: 141:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:
GGGAGGACGA UGCGGGACCN UUGUNUGCGA UUCAACUCGU AGGUCUUCUC 50
ACGUGCAGAC GACUCGCCCCG A 71
- (2) INFORMATION FOR SEQUENCE ID NO: 142:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 69 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:
GGGAGGACGA UGCGGUUAUG GGCGUCAACA CCGCUAUUAC AACUUUCGCC 50
CCCCAGACGA CUCGCCCCGA 69

(2) INFORMATION FOR SEQUENCE ID NO: 143:
(i) SEQUENCE CHARACTERIZATION:
(A) LENGTH: 70 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULAR TYPE: RNA
(ix) FEATURE:
(D) OTHER INFORMATION: All pyrimidines are 2'-F modified
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 143:
GGGAGGACGA UGCGGUUAUG GGUGUCAACA CCGCUAUUAC AACUUUCGCC 50
UCCCCAGACG ACUCGCCCCGA 70

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05964

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07H 21/02

US CL : 536/24.3, 22.1, 23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/24.3, 22.1, 23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

GenEmbl, EST,N_Geneseq, Pending Patents_NA, Issued Patents_NA; search: OLIGO_NUC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 5,731,144 A (TOOTHMAN et al.) 24 March 1998, see entire document	1
A,P	US 5,731,424 A (TOOTHMAN et al.) 24 March 1998, see entire document, especially claims	1



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

B earlier document published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z

document member of the same patent family

Date of the actual completion of the international search

08 MAY 1999

Date of mailing of the international search report

27 MAY 1999

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